The American Journal of CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

Copy 2
Lane Library
LANE MEDICAL LIBRARY
AUG 5 1961

Convention Issue

A PUBLICATION OF THE Yorke GROUP

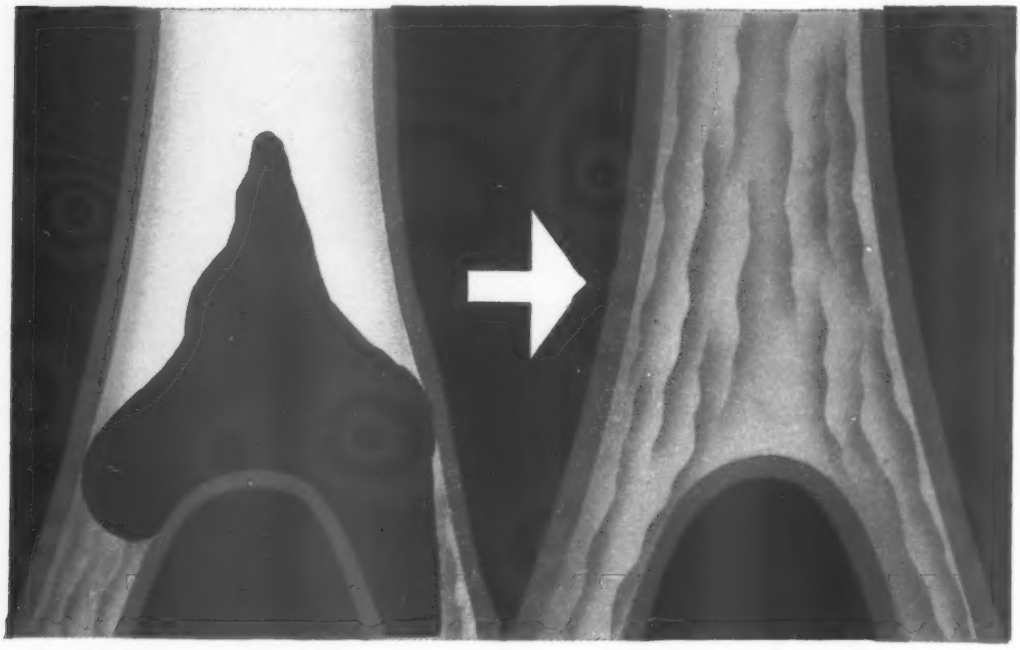
MAY 1961

clinical endorsement grows as proof accumulates

ACTASE
TRADEMARK

Fibrinolysin (Human)

NOT JUST A NEW DRUG...*A NEW THERAPY*



Ortho

SPECIFIC FOR THE DISSOLUTION
OF INTRAVASCULAR CLOTS

For matched tubular diuresis

IN BOTH PROXIMAL AND DISTAL SEGMENTS

HYDROCHLOROTHIAZIDE
acts mainly in the proximal segments of the renal tubules.

ALDACTONE® (spironolactone)
acts mainly in the distal segments of the renal tubules.

NEW

ALDACTAZIDE®

(brand of spironolactone with hydrochlorothiazide)

ALDACTAZIDE now offers physicians the only therapeutic preparation to provide positive diuretic activity in both the *proximal* and the *distal* segments of the renal tubules.

Hydrochlorothiazide exerts a well-known, vigorous diuretic action in the *proximal* segment of the renal tubules. The Aldactone component of Aldactazide specifically blocks the sodium-retaining and potassium-excreting effect of aldosterone in the *distal* segment.

This combined control provides true multiple diuretic effects for optimal relief of edema and ascites in patients requiring prompt, maximal control, and in those whose edema and ascites are resistant to single diuretics. Further, the potassium-saving activity in Aldactazide largely or wholly offsets the danger of potassium loss which thiazide diuretics induce.

The usual *adult* dose of Aldactazide is one tablet four times daily, although dosage may range from one to eight tablets daily.

Aldactazide is supplied as compression-coated white tablets, each tablet containing 75 mg. of Aldactone (brand of spironolactone) and 25 mg. of hydrochlorothiazide.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
Research in the Service of Medicine

NOW...
A DRUG THAT LOWERS CHOLESTEROL LEVELS AS MUCH AS 200 mg.%
WITH NO ANNOYING SIDE EFFECTS IN 80% OF PATIENTS...AND NO DIETARY RESTRICTIONS

NICALEX*

TABLETS aluminum nicotinate Walker

New NICALEX reduces blood cholesterol levels as much as 200 mg. % with no flushing, itching or gastrointestinal disturbance in 80% of patients.[1-4] Significant reductions have been obtained in close to 90% of hypercholesteremic patients to date.[1-4] Lowered cholesterol levels can be maintained indefinitely with little or no discomfort to most patients. And there is no need to restrict the diet throughout therapy.

A newly synthesized salt of nicotinic acid, NICALEX is "...as effective in reducing blood cholesterol as plain nicotinic acid...."[5] But unlike the older therapy, which produces vasomotor and gastrointestinal side effects in the vast majority of patients, NICALEX is characterized by a markedly reduced incidence of unpleasant reactions.[1-5]

NICALEX is so well tolerated because it is hydrolyzed *slowly* and *uniformly* in the gastrointestinal tract into aluminum hydroxide, an effective buffering agent, plus active nicotinic acid. Thus, a sustained cholesterol-lowering action can be readily maintained with a lower incidence of unwanted effects.

Dosage: 2 to 4 tablets t.i.d., with or after meals. Each tablet contains aluminum nicotinate Walker equivalent in activity to 500 mg. of nicotinic acid.

Supplied: Bottles of 100 and 1000.

References: 1. Tandowsky, R. M.: Personal communication. 2. Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. 3. Thompson, C. E.: Personal communication. 4. Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. 5. Hobbs, T. G.: Personal communication.

*PAT. PENDING

Walker LABORATORIES, INC., MOUNT VERNON, N. Y.

Symbol of Distinguished Journalism

The American Journal of Cardiology

Editor-in-Chief

SIMON DACK, M.D., NEW YORK

Associate Editors

SAMUEL BELLET, M.D., PHILADELPHIA
ALDO A. LUISADA, M.D., CHICAGO
ASHTON GRAYBIEL, M.D., PENSACOLA
GEORGE R. MENEELY, M.D., NASHVILLE
MYRON PRINZMETAL, M.D., LOS ANGELES

Assistant Editors

RAYMOND HARRIS, M.D., ALBANY
LESLIE A. KUHN, M.D., NEW YORK

EDITORIAL CONSULTANTS

Osler A. Abbott, M.D., *Atlanta*
Mariano M. Alimurung, M.D., *Manila*
Charles P. Bailey, M.D., *New York*
Claude S. Beck, M.D., *Cleveland*
Richard J. Bing, M.D., *Detroit*
Benjamin Boshes, M.D., *Chicago*
Ignacio Chavez, M.D., *Mexico City*
Eduardo Coelho, M.D., *Lisbon*
Pedro Cossio, M.D., *Buenos Aires*
J. Frank Dammann, Jr., M.D., *Charlottesville*
David B. Dill, M.D., *Aberdeen, Md.*
Felix G. Fleischner, M.D., *Boston*
Benjamin M. Gasul, M.D., *Chicago*
John W. Gofman, M.D., *Berkeley*
Emanuel Goldberger, M.D., *New York*
E. Magalhaes Gomes, M.D., *Rio de Janeiro*
Donald E. Gregg, M.D., *Washington*
Arthur Grishman, M.D., *New York*
Arthur C. Guyton, M.D., *Jackson*
W. F. Hamilton, PH.D., *Augusta*
R. Heim de Balsac, M.D., *Paris*
Martti J. Karvonen, M.D., *Helsinki*
Bruno Kisch, M.D., *New York*
Ray W. Kissane, M.D., *Columbus*
H. W. Knipping, M.D., *Cologne*
John C. Krantz, Jr., M.D., *Baltimore*
John S. LaDue, M.D., *New York*
Philip R. Lee, M.D., *Palo Alto*
Maurice Lev, M.D., *Chicago*
Samuel A. Levine, M.D., *Boston*
William Likoff, M.D., *Philadelphia*
K. I. Melville, M.D., *Montreal*
M. Carlos Monge, M.D., *Lima*
John H. Moyer, M.D., *Philadelphia*
Alexander S. Nadas, M.D., *Boston*
John L. Patterson, Jr., M.D., *Richmond*
Arrigo Poppi, M.D., *Bologna*
Walter S. Priest, M.D., *Chicago*
Wilhelm Raab, M.D., *Burlington*
Fernando Herrera Ramos, M.D., *Montevideo*
Stanley J. Sarnoff, M.D., *Bethesda*
G. W. H. Schepers, M.D., *Wilmington*
David Scherf, M.D., *New York*
Hans Selye, M.D., *Montreal*
Louis H. Sigler, M.D., *Brooklyn*
Demetrio Sodi-Pallares, M.D., *Mexico City*
Pierre Soulié, M.D., *Paris*
Paul Wood, M.D., *London*
Henry A. Zimmerman, M.D., *Cleveland*

THE AMERICAN JOURNAL OF CARDIOLOGY is published monthly by The Reuben H. Donnelley Corporation, Executive and Editorial Offices, 466 Lexington Avenue, New York 17, N. Y. May 1961, Volume 7, No. 5. Copyright © 1961 by The Reuben H. Donnelley Corporation. No part of the contents of this publication may be reproduced or distributed without the express written consent of the publishers. Publication Office, 20th and Northampton Streets, Easton, Pa. Second-class postage paid at Easton, Pa. Official Journal of the American College of Cardiology.

SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $15.00
SINGLE COPIES: Regular Issues $2.00; Symposium and Special Issues $4.00

MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. Change of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted in duplicate to the Editorial Office of The American Journal of Cardiology, 466 Lexington Avenue, New York 17, N. Y. The top should be indicated on the back of each photograph. Reference style: Smith, J. S. Treatment of cardiac failure. *Am. J Cardiol.*, 3: 274, 1959.

AMERICAN COLLEGE OF CARDIOLOGY: All communications for the College should be addressed to the American College of Cardiology, Office of the Executive Director, 350 Fifth Ave., New York 1, N. Y.

PLINY A. PORTER—Publisher
JOHN J. MARTIN—Assistant Publisher

new

"flavor-timed"

dual-action

coronary vasodilator

Dilcoron

TRADEMARK

ORAL

for **Sustained** *coronary vasodilation and protection against anginal attack*

SUBLINGUAL

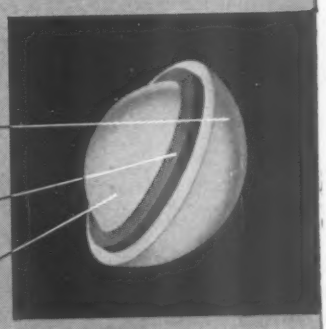
for **Immediate** *relief from anginal pain*

DILCORON contains two highly efficient vasodilators in a unique core-and-jacket tablet.

Glyceryl trinitrate (nitroglycerin)—0.4 mg. (1/150 grain) is in the outer jacket—held under the tongue until the citrus flavor disappears; provides rapid relief in acute or anticipated attack.

The middle layer of the tablet is the citrus "flavor-timer."

Pentaerythritol tetranitrate—15 mg. (1/4 grain) is in the inner core—swallowed for slow enteric absorption and lasting protection.

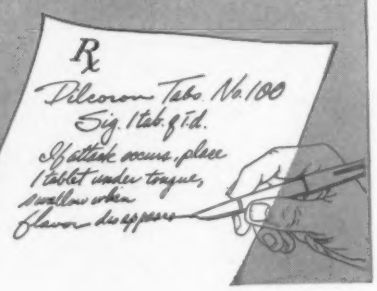


Bottles of 100.

For continuing prophylaxis patients may swallow the entire Dilcoron tablet.

Average prophylactic dose: 1 tablet four times daily.

Therapeutic dose: 1 tablet held under the tongue until citrus flavor disappears, then swallowed.



Winthrop LABORATORIES
NEW YORK 18, N. Y.

The American Journal of Cardiology

Volume VII MAY 1961 Number 5

CONTENTS

Clinical Studies

The Vectorcardiogram in Incomplete Left Bundle Branch Block 629
CELESTINO SANCHEZ, THOMAS J. WALSH AND EDWARD MASSIE

In incomplete left bundle branch block the vectorcardiographic QRSsÊ loop is usually oriented to the left, anteriorly and inferiorly with some conduction delay in the initial deflection or other portions of the loop. A characteristic figure of eight configuration and posterior rotation of the horizontal loop QRSeÊ were also of diagnostic value.

The Vectorcardiogram in Left Bundle Branch Block 638
RAFAEL LUNA AND ALBERT JACKSON

Vectorcardiograms of thirty patients with left bundle branch block are analyzed, explained and correlated with ventricular activation. Characteristically the initial component of the QRS loop is directed anteriorly and to the left. Conduction delay is best seen in the plateau and centripetal portion of the R loop.

The Electrocardiogram, Vectorcardiogram and Ventricular Gradient in Combined Pulmonary Stenosis and Interatrial Communication 646
GEORGE E. BURCH AND NICHOLAS P. DEPASQUALE

In valvular pulmonary stenosis with left to right shunts, the electrocardiogram resembles that found in uncomplicated atrial septal defect. In patients with right to left shunt it is similar to that in pulmonary stenosis; the vectorcardiogram in many patients showed QRSsÊ loop oriented superiorly, to the right and posteriorly. This pattern is not seen in tetralogy of Fallot.

The Clinical Value of Vectorcardiography 657
EDWARD W. HECKERT, WILLIAM R. COOK AND SEYMOURE KRAUSE

Vectorcardiographic studies of 1,000 adult patients show that the cube and tetrahedron systems are useful supplements to the twelve lead electrocardiogram. The tetrahedron system revealed abnormalities better than the cube system in right ventricular hypertrophy, combined left and right ventricular hypertrophy, inferior myocardial infarction and posterior myocardial infarction. The cube system was superior in cases of anterior myocardial infarction, left ventricular hypertrophy, left bundle branch block and right bundle branch block.

The Electrocardiogram in Marfan's Syndrome 661
DORRANCE BOWERS

Marfan's syndrome is an abiotrophic disorder of the cardiovascular system frequently associated with nonspecific electrocardiographic abnormalities.

Contents continued on page 7

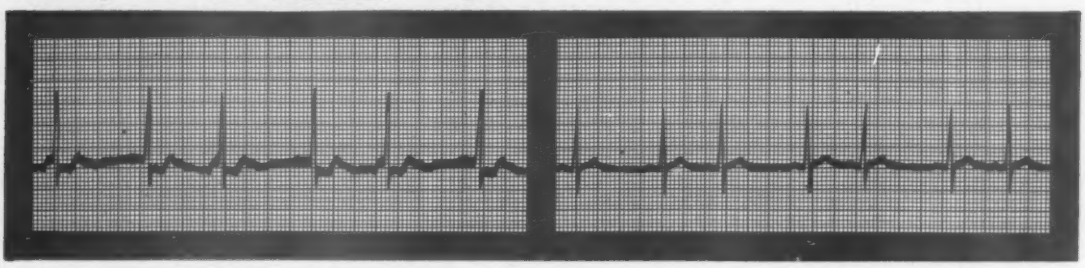
in coronary artery disease

with or without angina

Peritrate is basic for both

because it produces a substantial and sustained increase in myocardial blood flow... without significant change in cardiac output, blood pressure, or pulse rate

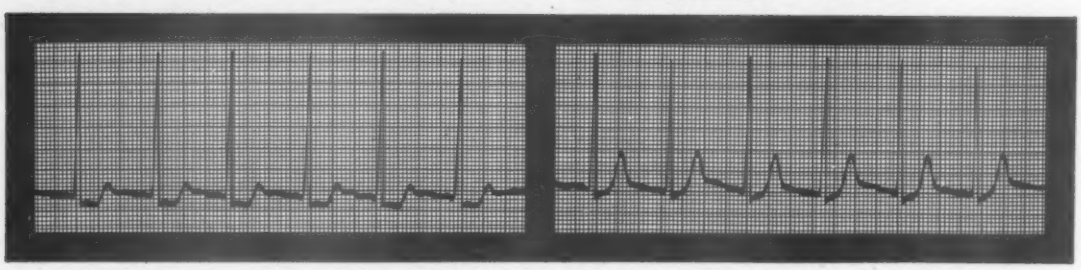
the patient [with] angina*



before **Peritrate**—S-T depression after standard exercise in anginal patient with no history of infarction.

after **Peritrate** (20 mg., administered 4 hours before exercise test). S-T segment near normal.

the postcoronary patient [without] angina*



before **Peritrate**—Abnormal ECG response to standard exercise in postinfarction patient without angina.

after **Peritrate** (20 mg., administered 90 minutes before exercise test). S-T segment near normal.

*Electrocardiograms and case histories on file in the Medical Department, Warner-Chilcott Laboratories.

Full dosage information, available on request, should be consulted before initiating therapy.

basic therapy in coronary artery disease
—with or without angina

Peritrate®

brand of pentaerythritol tetranitrate

Watch your mail for the ECG Interpretation Series

WARNER CHILCOTT

MORRIS PLAINS, N.J.

makers of Tedral Gelusil Proloid Mandelamine

GP 12 REV 1

Serum Glutamic Oxalacetic Transaminase Activity in Acute Coronary Thrombosis with Myocardial Infarction. Relation to Prognosis 673
MARSH MCCALL, ARTHUR HERTZ, IRVING RAPPAPORT AND WILLIAM NELSON

Results of SGO-T studies in 186 patients with acute transmural myocardial infarction confirm its diagnostic and prognostic value. Patients with higher SGO-T values had higher mortality rates.

Oral I^{131} Triolein Tolerance Curves in Elderly Subjects with Coronary Artery Disease . 676
JERRY EDELMAN, HERSCHEL SANDBERG, EDWARD R. DICKSTEIN AND SAMUEL BELLET

Oral I^{131} triolein tolerance curves reveal that older people have poorer lipid absorption than younger persons.

Cardiac Arrhythmias Following Intracardiac Surgery 681
MICHAEL D. RABBINO, LEONARD S. DREIFUS AND WILLIAM LIKOFF

After intracardiac surgery significant arrhythmias developed in thirty-nine patients (18.5 per cent). The most serious problems occurred in either overdigitalized or underdigitalized persons. Most common were atrial fibrillation and nonparoxysmal nodal tachycardia.

Experimental Studies

The Effect of Experimental Hypothyroidism on Coronary Blood Flow and Hemodynamic Factors 690
JOHN C. SCOTT, THEODORE A. BALOURDAS AND MILLARD N. CROLL

In dogs with experimentally produced hypothyroidism, a reduction in coronary sinus blood flow, left ventricular oxygen consumption and heart rate was observed. Administration of atropine increased these values to a level equal to that produced by atropine in normal control dogs, presumably due to changes in heart rate. The capacity of the hypothyroid heart to change its rate appears to be unimpaired.

Effect of Reserpine on Tachycardia Induced by Thyroid in the Isolated Atrium of the Rat 694
IRWIN E. MENDELSOHN, ARTHUR BASSETT, JOHN J. KELLY, JR. AND BRIAN F. HOFFMAN

Using isolated rat atria these investigators conclude that catecholamines mediate the tachycardia induced by thyroid hormone.

Contents continued on page 9

Proven

in over six years of clinical use and
more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . . .

Meprospan®

Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

WALLACE LABORATORIES / *Cranbury, N. J.*

CONTENTS continued—May 1961

VOLUME SEVEN NUMBER FIVE

QRS Alterations Produced by Auricular and Ventricular Paroxysmal Tachycardia in the Presence of Bundle Branch Block Patterns. An Experimental Study in Dogs 697
OTTO F. MULLER, MANUEL CARDENAS AND SAMUEL BELLET

QRS complexes in ventricular tachycardia may show complete bundle branch block pattern when they occur between T and P waves or narrowed, relatively normal complexes when they fall during the P-R interval.

Report on Therapy

The Use of Vasopressors in Cardiac Arrhythmias, Particularly Ventricular Tachycardia 707
WALDO GREENSPAN AND ZARIE L. SHAHGALDIAN

Vasopressors can effectively end ventricular tachycardias in the presence of shock, provided a critical level of systolic blood pressure (180–190 mm. Hg) is not exceeded.

Review

Idiopathic Myocardial Hypertrophy 714
MARVIN A. SACKNER, DAVID H. LEWIS, MORTON J. ROBINSON AND SAMUEL BELLET

The records of twenty-one adult patients with idiopathic myocardial hypertrophy suggest this diagnosis should be suspected when cardiomegaly occurs in relatively young normotensive men with gallop sounds, absent organic murmurs, and electrocardiographic evidence of left atrial and left ventricular enlargement irrespective of congestion.

Case Reports

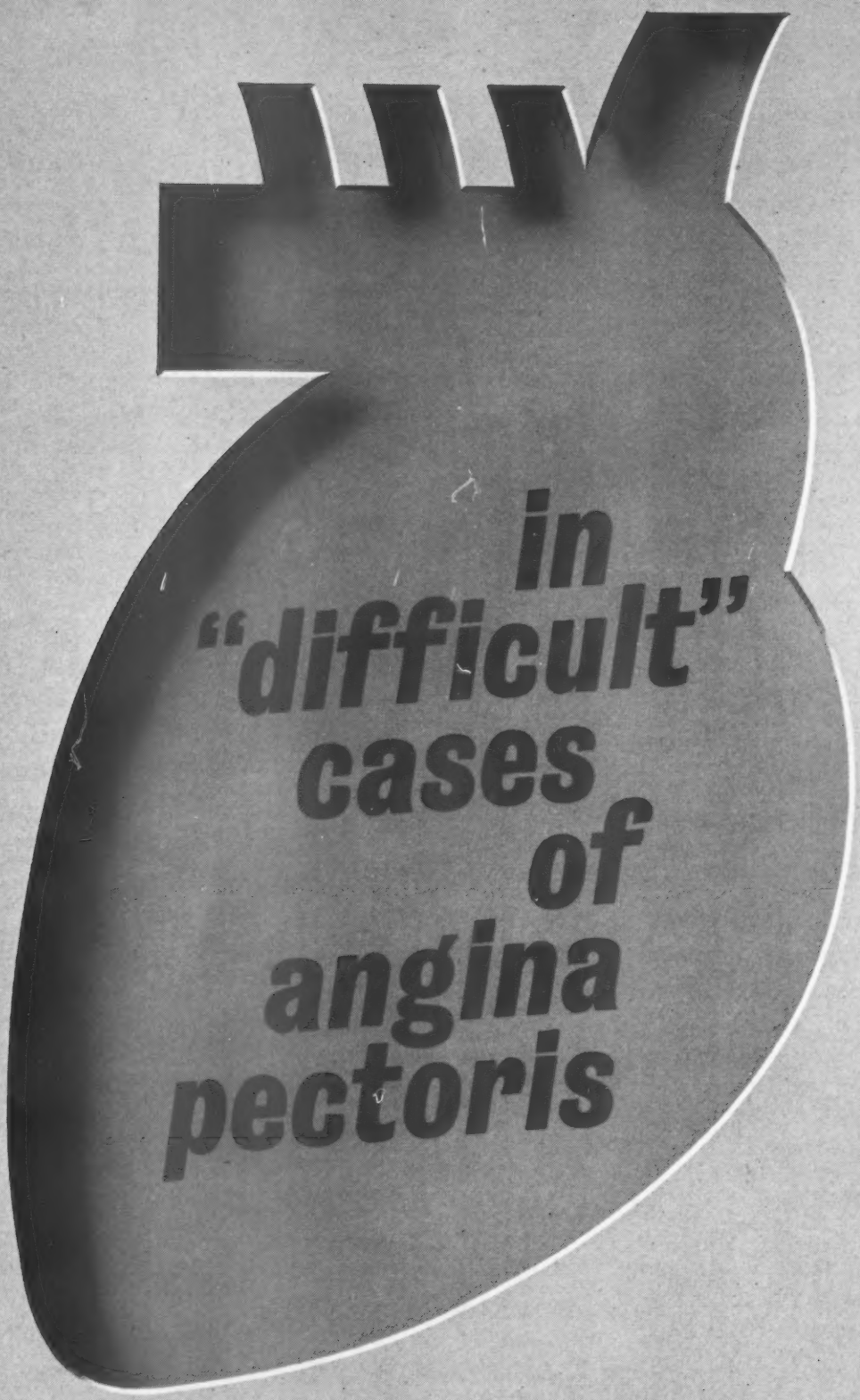
Resuscitation from Ventricular Fibrillation Complicating Acute Coronary Occlusion. Report of a Case 724
ELLIS L. ROLETT

This is the ninth reported case of successful open chest cardiac resuscitation in acute coronary occlusion complicated by ventricular fibrillation.

Closed Chest Cardiac Resuscitation in Acute Myocardial Infarction 731
F. JOSEPH THAL, MARIA E. CERNY, DONALD J. CONLON, MARVIN A. YUSSMAN AND ROBERT H. IRWIN

This is a successful case of closed chest cardiac resuscitation of a patient who had ventricular fibrillation following acute myocardial infarction.

Contents continued on page 11



Marplan

prevents anginal pain[1-4]
increases exercise tolerance[2,5,6]
reduces nitroglycerin requirements[2,3]

A potent regulator of amine oxidase, Marplan has demonstrated a high degree of effectiveness in moderately severe to intractable angina pectoris. Improvement on Marplan ranged from a reduction in the number of attacks to virtual abolition of the anginal state. With Marplan, anginal relief is enhanced by a more confident mental climate — improving the chances of success of the entire prophylactic regimen. However, since the precise manner in which Marplan improves the cardiac status is as yet undefined, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy. Consult literature and dosage information, available on request, before prescribing.

References: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Obiath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, Virginia M. Month., 87:23, 1960. 4. T. Winsor and P. Zarco, Angiology, 11: (Part 2), 67, 1960. 5. G. C. Griffith, Clin. Med., 6:1555, 1959. 6. C. C. Griffith, Dis. Nerv. System, 21 (Suppl.), 101, 1960.

MARPLAN® — 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

ROCHE
ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.

CONTENTS continued—May 1961

VOLUME SEVEN NUMBER FIVE

Cardiac Resuscitation after Documented Myocardial Infarction. Case Report of a "Successful Failure" 736
DAVID J. TURELL AND MAJ. ELIAS A. HUSNI

Open heart massage restored life to a forty year old soldier with acute myocardial infarction. Surviving the complications of anoxic brain damage and peripheral arterial embolism, the soldier eventually died from septicemia.

Successful Treatment of Ventricular Fibrillation with Intracardiac Potassium Chloride 742
LEONARD WEINSTOCK AND CAPT. JAMES H. CLARK

Intracardiac potassium chloride and open cardiac massage successfully ended ventricular fibrillation in a three year old child undergoing a herniorrhaphy.

Use of Isoproterenol in the Treatment of Complete Heart Block Complicating Acute Myocardial Infarction 746
JOHN H. K. VOGEL

Complete heart block in patients with acute myocardial infarction can be successfully treated by continuous intravenous use of isoproterenol.

Atrial Flutter with 1:1 A-V Conduction 753
GEORGE A. RUBEIZ AND SAMI KAID BEY

The importance of rest and sedation in the treatment of cardiac arrhythimias is well demonstrated in this patient with atrial flutter who had 1:1 atrial flutter after exercise.

Special Departments

Workmen's Compensation for the Cardiac 757
Progress Notes in Cardiology 761
College News 763

Index to Advertisers on pages 59 and 60

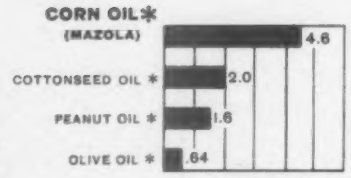
Of all leading brands
of vegetable oils...

Mazola®
liquid corn oil
is best for replacing saturated fats

because Mazola is both unexcelled in polyunsaturates (that reduce serum cholesterol) and lowest in saturates (that raise serum cholesterol).

HERE'S PROOF:

This chart shows that the ratio of polyunsaturates to saturates provided by Mazola Corn Oil is more than twice that of any other leading vegetable oil.



*U. S. Dept. of Agriculture Reports—1959

Your patients will find Mazola Corn Oil ideally suited for salad dressings, baking and frying. By instructing them to use Mazola in place of a substantial portion of more saturated types of fat, and to watch their caloric intake, you frequently will be able to lower the serum cholesterol with minimum changes in eating habits.

MAZOLA CORN OIL IS ALSO AVAILABLE IN CANADA, WESTERN EUROPE, LATIN AMERICA AND MANY OTHER COUNTRIES THROUGHOUT THE WORLD

COMPOSITION OF MAZOLA CORN OIL

Mazola Corn Oil has the following average composition:

Fatty Acids	Grams/ 100 grams	Grams/ fl. oz. (2 tablespoons)
Polyunsaturates...	52-58	14-15.7
Monounsaturates..	28-36	7.5-9.7
Saturates	10-14	2.8-3.8
Natural Sitosterols...	1 (0.9-1.3)	0.14
Natural Tocopherols..	about 0.1	0.015
Cholesterol	none	none
Salt (Sodium chloride)	none	none

Calories—125/tablespoon
Iodine value—124 average

CORN OIL CONTINUES TO BE A PREFERRED VEGETABLE OIL IN NUTRITIONAL STUDIES OF HYPERCHOLESTEROLEMIA.

FREE!

Valuable aid for guiding your hypercholesterolemic patient in dietary control: **A Pad of Menu Guides** based on 2,000 calories per day, with which you may readily construct a diet pattern best suited to your patient's needs.

Just write on your letterhead to:
CORN PRODUCTS COMPANY,
10 EAST 56 STREET, NEW YORK 22, N. Y.

PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY; material is copyrighted and may not be reproduced without permission of the publishers.

Preparation of Manuscripts

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editor; include staff position and connection; list bibliographic references in chronological order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical, with volume, page and year. For example: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3:274, 1959.

Preparation of Illustrations

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

Reviews, Abstracts

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

Reprints

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology,** 466 Lexington Avenue, New York 17, N. Y. Prices are quoted after articles are published.

The American Journal of Cardiology

466 Lexington Avenue, New York 17, New York

TO RESTORE NORMAL CARDIAC RHYTHM... A NEW HIGH LEVEL IN QUINIDINE THERAPY!

CARDIOQUIN®

Quinidine Polygalacturonate, Purdue Frederick

TABLETS

SMOOTHLY MAINTAINED THERAPEUTIC BLOOD LEVELS are an outstanding advantage of quinidine polygalacturonate.[1] Measurable blood levels appear within 1 hour, reach full therapeutic range in 4 to 6 hours,[2] and remain uniformly constant with maintenance doses.

CLINICAL STUDIES SHOW NO "PEAKS AND VALLEYS," typical of the multiple doses of other quinidine preparations (quinidine sulfate, quinidine gluconate, etc.).[3,4] 'Cardioquin' Tablets produce more uniform blood levels with but a single peak and a *slow, gradual decline* over 24-48 hours.[1]

UNIFORM RATE OF ABSORPTION is *inherent* in the molecular structure of quinidine polygalacturonate. 'Cardioquin' Tablets are *not* sustained-release tablets, nor do they depend on mechanical contrivances such as enteric coating.[1,2]

OUTSTANDING GASTROINTESTINAL TOLERANCE to 'Cardioquin' Tablets is due to their slow, steady rate of dissociation, which avoids the irritating flooding of the gastrointestinal tract with inorganic ions. Moreover, the unabsorbed polygalacturonate moiety acts as a buffer and a demulcent.[1,2] *'Cardioquin' Tablets therapy is virtually free of the undesirable gastrointestinal reactions common to quinidine, such as diarrhea, nausea, and vomiting.*[1,2,5,6]

FULL QUINIDINE CARDIODYNAMICS of 'Cardioquin' Tablets are demonstrated, on the dose for dose basis, by ECG changes[1,2,5] and by a high percentage of successful conversions of arrhythmias.[1,5,6]

WIDER RANGE OF EFFECTIVENESS is possible with 'Cardioquin' Tablets, because their unprecedented gastrointestinal tolerance permits extension of quinidine therapy to many patients intolerant of ordinary quinidine salts.[1,6]

NOTE: Each 'Cardioquin' Tablet contains the quinidine-equivalent of the conventional three-grain tablet of quinidine sulfate, thus providing facility in dosage calculation or substitution for other quinidine salts. 'Cardioquin' Tablets may be substituted one tablet for each three-grain quinidine sulfate tablet (or equivalent) previously administered.

Consult Product Data Brochure, available on request, for complete directions, contraindications and precautions attending the use of the drug.

REFERENCES: 1. Shaftel, N., Halpern, A.: Am. J. Med. Sci. 236:184 (Aug.) 1958. 2. Halpern, A., Shaftel, N., Schwartz, G.: Antibiot. & Chemother. 9:97 (Feb.) 1959. 3. Sokolow, M., Edgar, A. L.: Circulation 12:576, 1950. 4. Bellet, S., Finkelstein, D., Gilmore, H.: A.M.A. Arch. Int. Med. 100:750 (Nov.) 1957. 5. Schwartz, G.: Angiology 10:115 (April) 1959. 6. Tricot, R., Nogrette, P.: Presse med 68:1085 (June 4) 1960.

The Purdue Frederick Company

DEDICATED TO PHYSICIAN AND PATIENT SINCE 1892

NEW YORK 14, N.Y. | TORONTO 1, ONTARIO

©COPYRIGHT 1961, THE PURDUE FREDERICK COMPANY

BOOTH 18
at the Convention

Noteworthy NEW BOOKS

F. A. DAVIS COMPANY

ARBEIT, RUBIN & GROSS'
DIFFERENTIAL DIAGNOSIS OF THE ECG

A new and rewarding method of utilizing the electrocardiogram is presented in this new book. You will have a "cardiac consultant" that speaks in the clear clinical terms of the cardiologist: How to form a specific ECG diagnosis and see the diagnostic significance of each deviation from the normal in every portion of the ECG. First, there is a meaty summary of important basic principles. Then comes the extensive section that thoroughly covers DIFFERENTIAL DIAGNOSIS. There are *509 illuminating illustrations!*

By SIDNEY R. ARBEIT, M.D., Seton Hall College of Medicine; IRA L. RUBIN, M.D., Columbia University; HARRY GROSS, M.D., Columbia University. 220 pages (9" × 12"), 509 illustrations. $10.50.

BAILEY'S CARDIAC SURGERY—1960-61

Dr. Charles P. Bailey and six other world authorities describe today's highly developed techniques in the surgical therapy of cardiac lesions. They give a definite statement of principles, helpful notes on the pathologic aspects, and a detailed description of technique in which each operation is delineated with great care and precision. This book is priceless for *288 handsome and effective illustrations* of heart surgery.

Edited by CHARLES P. BAILEY, M.D., Chairman and Professor of Surgery, New York Medical College, Flower and Fifth Avenue Hospital, New York. 187 pages, 288 illustrations. In durable, flexible binding. $5.00.

MENDELSON'S CARDIAC DISEASE IN PREGNANCY

Pregnancy complicated by cardiac disease. . . the unique problems involved are now taken up in an important new book that presents the full experience of a recognized leader, vital notes on the total care of the obstetric cardiac patient. Dr. Mendelson demonstrates how the challenge of maternal mortality can be met when the specialties concerned are usefully integrated.

By CURTIS LESTER MENDELSON, M.D., F.A.C.S., F.I.C.S., Director, Obstetric Cardiac Clinic, New York Lying-in Hospital. 401 pages, 141 illustrations. $13.50.

PAGE'S ARTERIAL HYPERTENSION

A world-renowned worker discusses the problem in its three basic aspects: (1) The clinical problem as seen at the bedside, (2) the underlying mechanism producing the disease, (3) the latest methods of treatment.

By IRVINE H. PAGE, M.D., Director of Research, Cleveland Clinic Foundation. 40 pages, illustrated. In durable, flexible binding. $2.00.

ELLINGSON'S MEDICAL PROBLEMS OF AIR TRAVEL

Dr. Ellingson's valuable summary offers clear-cut advice on physical standards, cardiology, noise protection, motion sickness, all the pertinent problems in Aviation and Space Medicine.

By HAROLD V. ELLINGSON, M.D., Medical Service School, USAF (ATC), Gunther Air Base, Ala. 32 pages. $2.00.

Mail this coupon TODAY!

F. A. DAVIS COMPANY, 1914 Cherry Street, Phila. 3, Pa. C-5

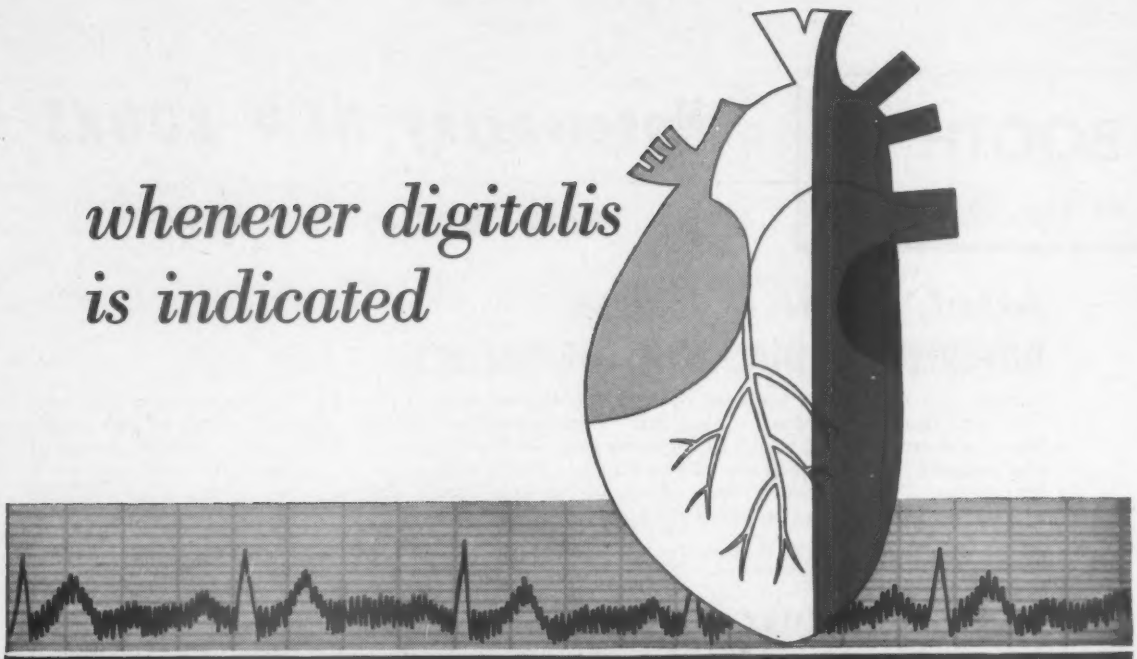
Send at once and charge to my account:

- ☐ Arbeit, Rubin & Gross' Differential Diagnosis of the Electrocardiogram, $10.50
- ☐ Bailey's Cardiac Surgery, $5.00
- ☐ Mendelson's Cardiac Disease in Pregnancy, $13.50
- ☐ Page's Arterial Hypertension, $2.00
- ☐ Ellingson's Medical Problems of Air Travel, $2.00

NAME..... ADDRESS.....

CITY..... STATE.....

whenever digitalis is indicated



'LANOXIN'® brand DIGOXIN

formerly known as Digoxin 'B. W. & Co.'®

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS
0.25 mg. scored (white)
0.5 mg. scored (green)

'LANOXIN' INJECTION
0.5 mg. in 2 cc. (I.M. or I.V.)

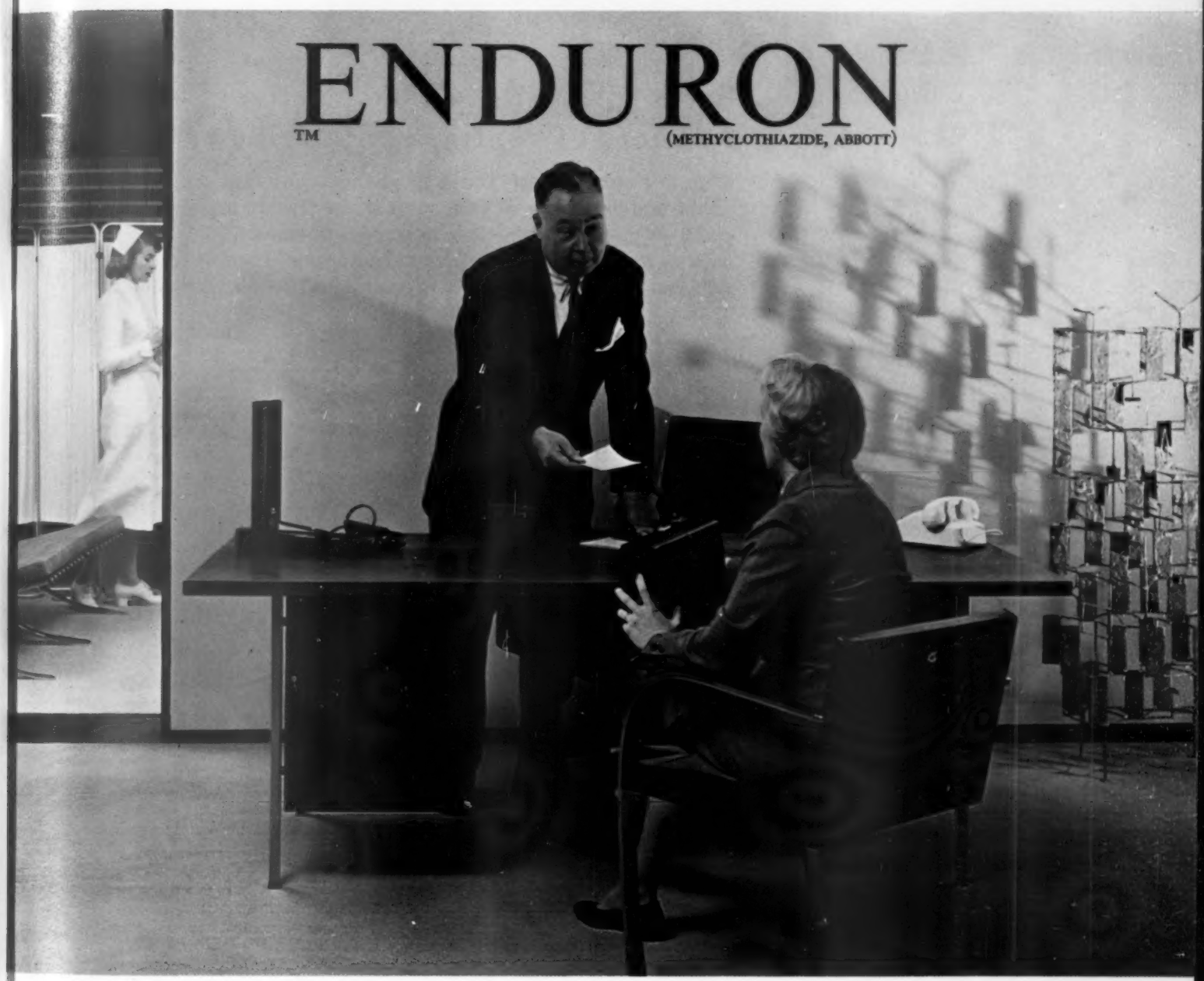
'LANOXIN' ELIXIR PEDIATRIC
0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

The 24-hour diuretic-antihypertensive

ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)



Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

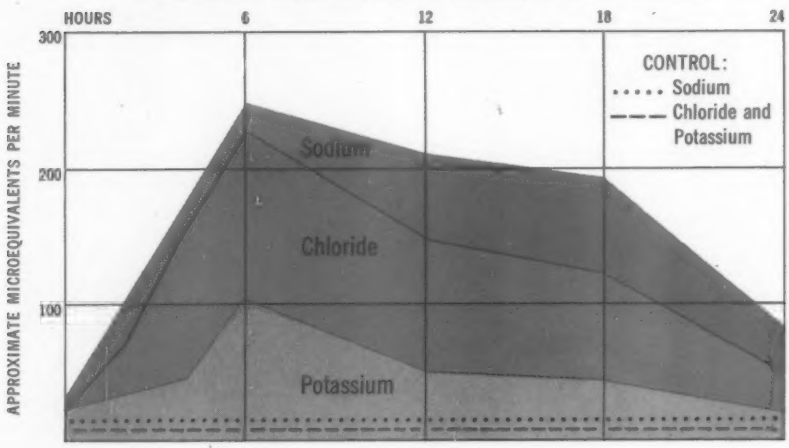
ABBOTT

104030A

Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

Usual Urinary Excretion Patterns Following 10 mg. of Enduron



Note that Enduron's effect on urinary potassium is minor; potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.

How safe is Enduron?

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.

Prescribe the 24-hour diuretic-antihypertensive:

ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

ABBOTT

1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

©1961, ABBOTT LABORATORIES

1040308

THE *Yorke* CREED

THE PURPOSE OF the Yorke Medical Group is to contribute to the improvement of human health and well being through the publication of medical research and experiences, as controlled by our Physician-Surgeon Editorial Boards. Our code of conduct shall be—

To obtain the most qualified personnel available to serve on our Editorial Staffs.

To select material only on the basis of its scientific merit and value to the profession and such selection shall be the sole and exclusive responsibility of the Physicians and Surgeons who comprise the Editorial Boards.

To limit advertising to ethical pharmaceuticals and reputable medical equipment or services of immediate interest to our subscribers. Advertising must be consistent in standards with the editorial policies of the Journals.

Medical journals present the recorded experiences of the profession and serve as a basis for new researches and life preserving developments.

THE YORKE GROUP
NEW YORK, N. Y.

THE AMERICAN JOURNAL OF SURGERY
THE AMERICAN JOURNAL OF MEDICINE
THE AMERICAN JOURNAL OF CLINICAL NUTRITION
THE AMERICAN JOURNAL OF CARDIOLOGY
MODERN DRUGS

BEFORE

LYOVAC®

THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

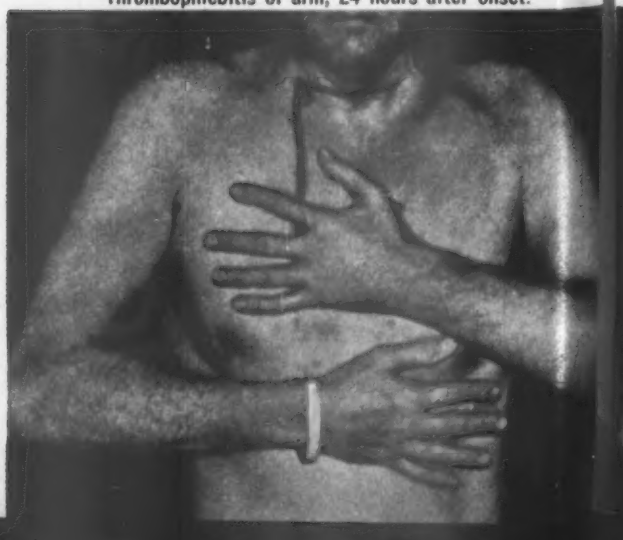
a new agent
for lysis of
vascular thrombi

Phlebothrombosis of femoral and iliac vein, 3 weeks after onset.

Superior vena cava thrombosis (8 hrs. after starting THROMBOLYSIN).

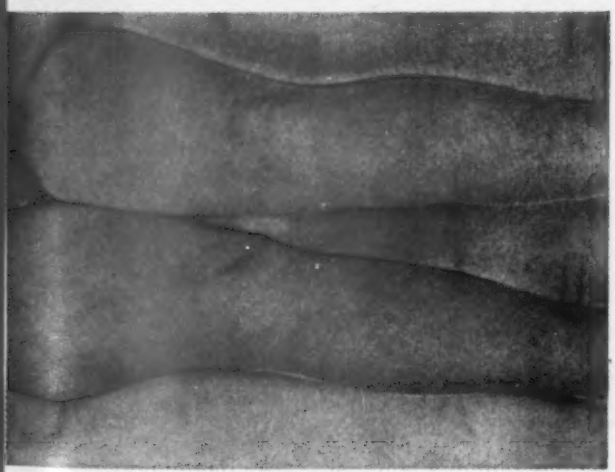
Phlebothrombosis (8 weeks' duration in left leg, 6 weeks' in right).

Thrombophlebitis of arm, 24 hours after onset.



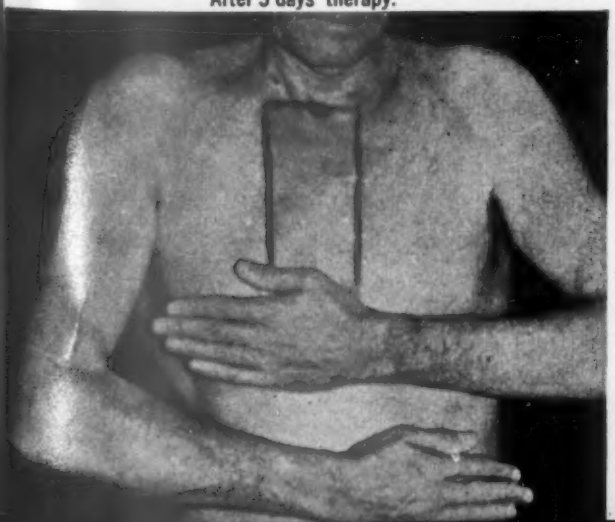
After 6 days' therapy.

After 3 days' therapy.



After 6 days' therapy.

After 5 days' therapy.



AFTER

LYOVAC®

THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)

in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi*, LYOVAC® THROMBOLYSIN makes possible

- lysis of formed clots
- reduced mortality and morbidity, shortened hospitalization
- reduced incidence of postphlebitic complications

with decreased incidence of reactions such as fever, chills, or malaise of severe proportions; higher degree of safety; greater, more predictable potency.

Supply: Each bottle contains 50,000 MSD units.

*See package circular for qualifications concerning cerebrovascular accidents and myocardial infarction.

Before prescribing or administering THROMBOLYSIN, *the physician should consult the detailed information on use accompanying the package or available on request.*

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

LYOVAC AND THROMBOLYSIN ARE TRADEMARKS OF MERCK & CO., INC.

Just Released

a Symposium on new methods of diagnosis and management of

Peptic Ulcer

Here is an outline of the contents:

. . . Formation of Hydrochloric Acid by the Stomach. The Current Status; C. ADRIAN M. HOGBEN . . . Vagal and Antral Mechanisms in Gastric Secretion; E. R. WOODWARD and LLOYD M. NYHUS . . . Influence of the Liver upon Gastric Secretion; JAMES S. CLARKE . . . The Pathologic Physiology of Peptic Ulcer; MORTON I. GROSSMAN . . . Geographical and Environmental Aspects of Peptic Ulcer; JACK D. WELSH and STEWART WOLF . . . Endocrine Tumors and Peptic Ulcer; ROBERT M. ZOLLINGER and THOMAS V. CRAIG . . . Peptic Ulcer in Primary Hyperparathyroidism; J. DONALD OSTROW, GERALD BLANSHARD and SEYMOUR J. GRAY . . . Ulcerogenic Drugs and Technics. Experimental and Clinical; HARRY L. SEGAL . . . Treatment of Peptic Ulcer. Current Concepts; JOSEPH B. KIRSNER and WALTER L. PALMER.

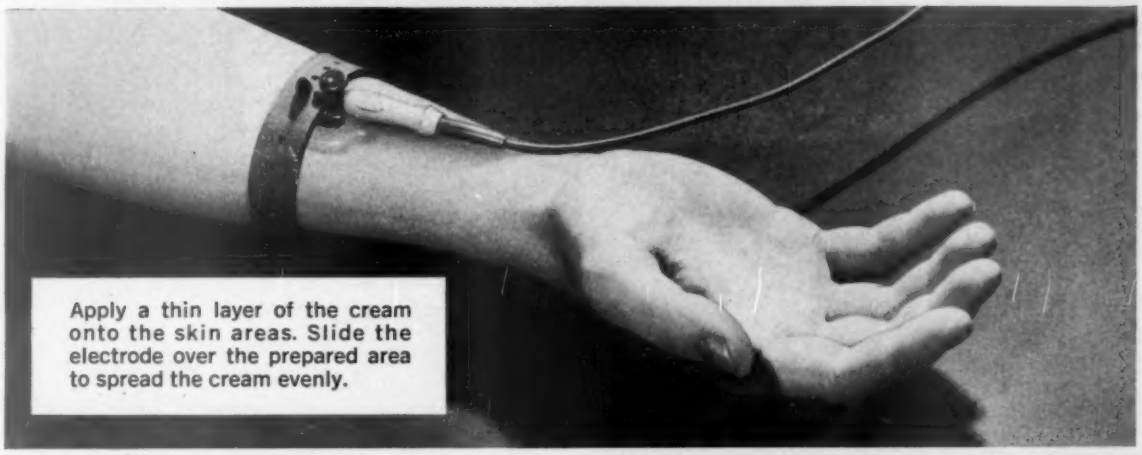
A limited edition of the Symposium on Peptic Ulcer is available at $3.00 per copy. Order now.

THE AMERICAN JOURNAL OF MEDICINE

466 Lexington Avenue • New York 17, New York

ATTENTION ALL EKG USERS

See How New electrell cream Disappears After Gentle Rubbing Into the Skin



Apply a thin layer of the cream onto the skin areas. Slide the electrode over the prepared area to spread the cream evenly.

After using, merely rub cream into skin or wipe with tissue. Will not corrode electrode contacts.

A cosmetically superior preparation, Electrell Cream solubilizes the skin oils, thus ensuring a good contact. Will not corrode electrodes. For use in electrocardiography and electro-encephalography.

DISTRIBUTED BY

General Electric

X-RAY DEPARTMENT

OFFICES IN PRINCIPAL CITIES

Send for FREE bottle today

General Electric X-ray Dept.
P. O. Box 172
Lafayette, Indiana

Please send me a free bottle of electrell cream.

Name .....

Address .....

City ..... Zone ..... State .....

ONLY QUINAGLUTE® DURA-TAB S.M.®

PROVIDES ORAL QUINIDINE GLUCONATE (5 gr.) ...BETTER TOLERATED

because it is 10 times as soluble as the sulfate

SAMPLES and literature—write...

REFER TO PDR Page 821

WYNN
PHARMACAL CORPORATION
Lancaster Ave. at 51st St.
Philadelphia 31, Pa.

*U.S. Patent 2,895,881

in q. 12 h. dosage each Sustained Medication* dose maintains uniformly effective, virtually non-fluctuating blood levels, all day, all night.

in cardiac arrhythmias for maximum quinidine efficacy, tolerance, convenience[1-5]—specify Quinaglute Dura-Tab S.M. Bottles of 30, 100 and 250.

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960.

also available: INJECTABLE QUINAGLUTE

Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

"nutrition . . . present as a modifying or complicating factor in nearly every illness or disease state."[1]

Theragran®

SQUIBB VITAMINS FOR THERAPY

clinically-formulated and potency-protected vitamins for your patients with cardiac disease who need therapeutic vitamin support

"Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2]

Each Theragran supplies the essential vitamins in truly therapeutic amounts:

Vitamin A	25,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units
Thiamine Mononitrate	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Vitamin C	200 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12}	5 mcg.

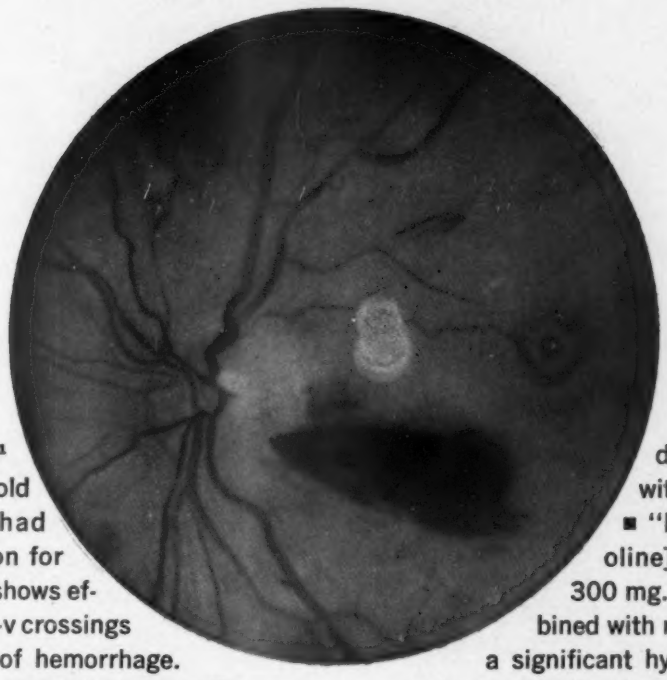
For full information see your Squibb Product Reference or Product Brief.

1. Youmans, J. B.: Am. J. Med. **25**:659 (Nov.) 1958.
2. Kampmeier, R. H.: Am. J. Med. **25**:662 (Nov.) 1958.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'Theragran'® is a Squibb Trademark

When blood pressure must come down



AS IN THIS CASE:[1] Fundus of 62-year-old female who has had severe hypertension for many years. Photo shows effect of pressure at a-v crossings and various types of hemorrhage.

■ When you see eyeground changes like this—with such hypertensive symptoms as dizziness and headache—your patient is a candidate for Serpasil-Apresoline. With this combination the antihypertensive action of Serpasil complements that of Apresoline to bring blood pressure down to near-normal levels in many cases. Side effects can be reduced to a minimum, since Apresoline is effective in lower dosage when given with Serpasil.

■ "Hydralazine [Apresoline] in daily doses of 300 mg. or less, when combined with reserpine, produced a significant hypotensive effect in a large majority of our patients with fixed hypertension of over three years' duration."[2]

Complete information sent on request.

SUPPLIED: Tablets #2 (standard-strength), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride. **Tablets #1** (half-strength), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride. /2832 MK

1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

CIBA
SUMMIT, N. J.

IN SHOCK OF MYOCARDIAL INFARCTION

INJECTION

ARAMINE®

(metaraminol)

"...A strong pressor effect with a myocardial-stimulating action in experimental studies."[1] "...Tens of thousands of intramuscular and subcutaneous injections. ... Not a single instance of tissue injury was observed."[2]

ARAMINE can be administered for pressor effect by any route—subcutaneous, direct intravenous, intramuscular, intravenous infusion. No slough reported **when injected into preferred vein of arm.** Minimal risk of causing arrhythmias.

Onset of action (intravenous): 1 to 2 minutes.

ARAMINE is always ready for immediate use—no dilution needed.

ARAMINE is also valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

Supplied: In 1-cc. ampuls and 10-cc. vials (10 mg. metaraminol present as the bitartrate per cc.).

ARAMINE is a trademark of Merck & Co., INC.

Additional information is available to physicians on request.

1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762, (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

MSD MERCK SHARP & DOHME, Division of Merck & Co., INC., West Point, Pa.

Cardiovascular patients respond in a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed – *often in two or three days.* He eats well, sleeps well and his depression no longer complicates your basic regimen.

Lifts depression...as it calms anxiety!

For cardiovascular patients–a smooth, balanced action that lifts depression as it calms anxiety...rapidly and safely

Balances the mood–no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly–the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly – often within two or three days.

Acts safely – no danger of hypotension. Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic cardiovascular therapy.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲

WALLACE LABORATORIES
Cranbury, N. J.

CD-7MB

LOWERING SERUM CHOLESTEROL for diabetic patients

Since linoleic acid is the principal polyunsaturated fatty acid in the vegetable oils which lower blood cholesterol, there seems to be no doubt that linoleic acid is the key factor in reducing serum cholesterol through diet. The facts are clearly stated in a recent JAMA editorial:

> "It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid ...they must replace rather than supplement some of the saturated fats and oils already in the diet."[2]

Very recent research indicates that use of Emdee Margarine in place of other spreads and shortenings may significantly contribute to reduction of serum cholesterol in diabetic patients,[1] as it has been observed to do in other patient groups.[3,4]

Emdee Margarine contains significantly more linoleic acid than any other margarine—including those promoted as "pure corn oil margarines." And, published scientific reports[3,4,5] attest to the value of Emdee Margarine in cholesterol-lowering diets. To date, no comparable studies with other margarines have been published.

EMDEE®
margarine
in place of other
shortenings
and spreads

REFERENCES:
1. Alterman, S. L.: Postgrad. Med. *28*:112 (Aug.) 1960.
2. Pollack, H.: J.A.M.A. *172*:1164 (Mar. 12) 1960.
3. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959.
4. Boyer, P. A., Jr.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.
5. Jolliffe, N.; Rinzler, S. H., and Archer, M.: Am. J. Clin. Nutrition *7*:451, 1959.

The linoleic acid-sparing process for manufacturing Emdee Margarine is unique (U.S. Patent No. 2,890,959). To protect flavor and texture, Emdee Margarine is packaged in cans and kept under refrigeration.

PITMAN-MOORE COMPANY DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

VERSATILE, PORTABLE SANBORN AMPLIFIER RECORDERS FOR BIOPHYSICAL RESEARCH

Any one of these portable amplifier recorders will provide your laboratory with greater recording flexibility and operating economy. Select either a one or two channel model with electronics for either DC or carrier amplification, for such applications as routine recording from transducers . . . monitoring output of laboratory instruments such as Sanborn "450" portable amplifiers (self-contained units with built-in power supplies, available in DC Coupling, Carrier, ECG/General Purpose, Low Level and other types), vital capacity spirometers, pH meters, etc. . . . or for direct-writing recording of one or two channels of a photographic recording system (e.g., Sanborn 564 and 558M) or a visual monitoring system (e.g., Sanborn 760 and 762).

FOR GENERAL PURPOSE DC RECORDING

The Model 299—21 lb., brief case, 1-channel recorder . . . 5 and 50 mm/sec or 2.5 and 25 mm/sec chart speeds . . . sensitivities from 10 volts to 10 mv/div . . . frequency response 0 to 100 cps, down 3 db at 10 div peak-to-peak . . . inkless recording.

Model 320—2 complete channels in a one-cubic-foot package — separate, current-feedback amplifiers with floating and guarded inputs . . . sensitivities from 2 volts to 0.5 mv/mm . . . full 50 mm for each channel . . . frequency response 0-125 cps, down 3 db at 10 mm peak-to-peak . . . choice of speed ranges—50, 25, 5, 2.5 mm/sec or 100, 20, 5, 1 mm/sec . . . inkless records. Model 322 also available, for low gain 2-channel recording.

FOR AC CARRIER AMPLIFIER RECORDING

Model 301 — single-channel portable — same construction, physical specifications and chart speed options as Model 299. Self-contained AC carrier amplifier recorder . . . sensitivities to 10 microvolts rms/div . . . frequency response 0-100 cps, down 3 db, 10 div peak-to-peak . . . internal 2400 cps carrier frequency . . . uncalibrated zero suppression. For similar applications but in *two channels*, Model 321 is available as a carrier amplifier version of the Model 320 system.

Contact your nearest Sanborn Branch Office or Service Agency for complete details, or write Research Instrument Sales Manager:

MEDICAL DIVISION

SANBORN COMPANY

175 Wyman St., Waltham 54, Massachusetts

POTENT CORONARY VASODILATOR PRODUCES GOOD RESPONSE IN 82.7% OF PATIENTS[1]

ISORDIL "...appears to exert a more consistent and profound effect than any drug previously employed for the prophylaxis of angina pectoris...Rapid onset of action and prolonged effect are additional clinical advantages."[1]

Isordil "...has been effective in about three-fourths of 51 patients with severe angina. Thirty-nine of the patients experienced either disappearance of the pain symptoms or substantial reduction in frequency and duration of attacks."[2]

Patients showed a dramatic decrease in the incidence and severity of angina pectoris and reported an increased sense of well being and a notable increase in exercise tolerance.[1]

Isordil's "...long duration of action and consistent marked activity establishes it as a most reliable drug for maintenance of dilatation of coronary vessels."[3]

Isordil "...appears to be the only agent currently available with marked sublingual as well as oral antianginal effectiveness."[4]

Dosage: average dose one 10 mg. tablet q.i.d.—a half hour before meals and at bedtime; dosage range 5-30 mg. q.i.d.; individualize dose for optimum therapeutic effect; use with caution in patients with glaucoma. Supplied: 10 mg. scored white tablets in bottles of 100.

1. Albert, A.: Isosorbide Dinitrate in Treatment of Angina Pectoris, Journal Lancet, *81*:112 (March) 1961. 2. Shapiro, S.: Angina Pectoris: Treatment with Isosorbide Dinitrate, Angiology *12*:53 (Feb.) 1961. 3. Leslie, R. E.: Coronary Vasodilators—A Comparative Study, Western Medicine *2*:56 (Feb.) 1961. 4. Russek, H. I.: Comparative Responses to Various Nitrates in the Treatment of Angina Pectoris, Journal of the Kansas City Southwest Clinical Society *36*:14 (Dec.) 1960.

ISORDIL®

FOR ANGINA PECTORIS

ISOSORBIDE DINITRATE

NOW AVAILABLE: ISORDIL WITH PHENOBARBITAL, THE ACCEPTED SEDATIVE FOR THE RELIEF OF ANXIETY IN HEART PATIENTS.

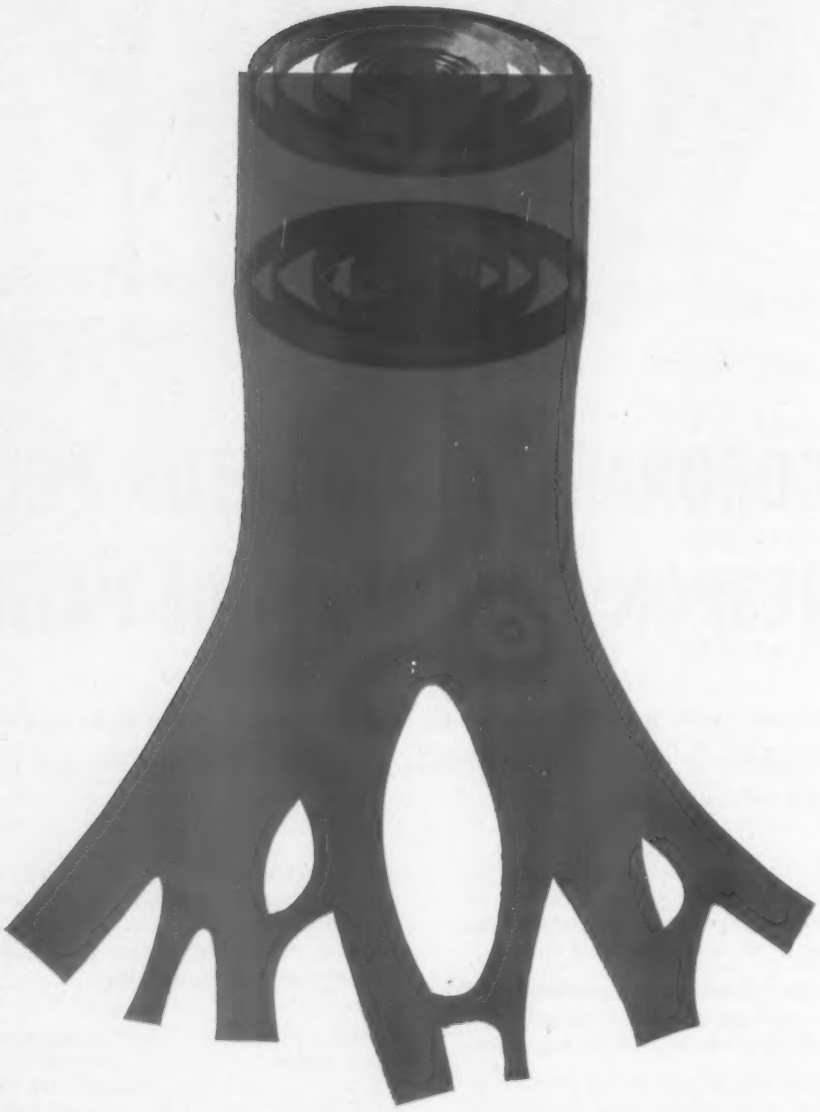
IVES-CAMERON COMPANY
New York 16, N. Y.

Literature and Professional Samples Available on Request

*TRADEMARK

Hygroton®
brand of chlorthalidone

in hypertension and edema, longer in action smoother in effect



Longer action[1] provides smooth, evenly-sustained therapeutic effect.[2] ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.[3] ■ Safeguards against significant potassium loss.[4] ■ Intensity of saluretic action enables liberalization of dietary salt restriction.[3] ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.[2]

References: 1. Ford, R. V.: Current Therap. Research 2:347, 1960. 2. Fuchs, M., and others: Current Therap. Research 2:11, 1960. 3. Ford, R. V.: Connecticut Med. 24:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. 56:343, 1960.

Detailed literature available on request.

Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York HY573-61 Geigy

REPRINT ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE

466 Lexington Avenue
New York 17, N. Y.

Please send me the following reprints from THE AMERICAN JOURNAL OF MEDICINE.

SEMINARS

☐ ALLERGY (1956)	$2.00
☐ DISEASE OF THE PANCREAS (1956)	$2.00
☐ BONE DISEASE (1957)	$2.00
☐ LIVER DISEASE (1958)	$2.00
☐ MYCOTIC INFECTIONS (1959)	$3.00

Enclosed is my check

Name _____

Address _____

City _____ State _____

new

AS TOMORROW!

BECK-LEE

Cardi-O-Mite

PORTABLE, DIRECT-WRITING
ELECTROCARDIOGRAPH

new **TRANSISTOR CIRCUITRY** for small size, only 11½" x 7½" x 6½"

new **LIGHT-WEIGHT PORTABILITY**—17-lb. unit ideal for office, hospital or house calls

new **AUDIBLE HEART SIGNAL**—built-in aural monitoring—first on any ECG

new **5CM RECORDING** — drop-in loading

new **SINGLE OR 2-SPEED MODELS**—slide-switch from 25 to 50 mm/sec.

new **HIGH INTERFERENCE-REJECTION RATIO** minimizes AC interference

new **VISUAL MONITORING WITHOUT USING PAPER**

Exclusive
2-YEAR GUARANTEE
on entire instrument and accessories

ASK FOR demonstration in your own office, no obligation

BECK-LEE Corporation
Dept. AJC561, 630 W. Jackson Blvd., Chicago 6, U.S.A.

For long-term control of hypertension, all the benefits of thiazide-rauwolfia therapy ...plus specific, physiologic vasodilation

Protoveratrine A vasodilation produces "the most physiologic, hemodynamic reversal of hypertension."[1] Only Salutensin offers your patient the advantages of protoveratrine A, a specific vasodilating agent, in combination with basic thiazide-rauwolfia therapy. Protoveratrine A is credited with producing "the most physiologic, hemodynamic reversal of hypertension."[1] It acts on the blood pressure reflex receptors[2-5] in the carotid sinus, heart and aorta to produce widespread peripheral vasodilation, increase renal blood flow, and relieve tachycardia. Because of the potentiating effect of Saluron, the diuretic component in Salutensin, the quantity of protoveratrine A in Salutensin is small enough to eliminate or reduce to a minimum the risk of unpleasant "veratrum" side effects.

A logical combination of actions, a single result: antihypertensive potentiation with reduced side effects. With Salutensin, you can resolve the problem of treating hypertension by means of this more logical antihypertensive approach—antipressor diuresis, mild sedation and specific peripheral vasodilation. Salutensin combines Saluron, a more effective 'dry-weight' diuretic which produces up to 60% greater excretion of sodium than does chlorothiazide;[9] reserpine, for mild tranquilizing and vasorelaxant effects; and protoveratrine A, to relieve arteriolar constriction and reduce peripheral resistance. The potentiating/additive effects of these antihypertensive agents[6,7,8,10-13] have been found to give a greater total therapeutic effect at dosage levels of each agent which *reduce the incidence and severity* of their side reactions.

Added advantages for long-term or difficult patients. Salutensin is indicated for almost every patient with essential hypertension who requires treatment. It will reduce blood pressure (both systolic and diastolic) to normal or near-normal levels, *and maintain it there,* in the great majority of cases. Patients on thiazide/rauwolfia therapy often experience further improvement when transferred to Salutensin. Patients who no longer respond to thiazide/rauwolfia may be spared the disturbing side effects of more potent antihypertensives by transferring them to Salutensin or by using Salutensin as their basic regimen. And Salutensin therapy is economical and convenient.

Each Salutensin tablet contains: 50 mg. Saluron (hydroflumethiazide), 0.125 mg. reserpine, and 0.2 mg. protoveratrine A. See Official Package Circular for complete information on dosage, side effects and precautions.

Supplied: Bottles of 60 scored tablets.

References: 1. Fries, E. D.: In Hypertension, ed. by J. H. Moyer, Saunders, Phila., 1959, p. 123. 2. Brest, A. N. and Moyer, J. H.: *J.A.M.A. 172*:1041 (Mar. 5) 1960. 3. Grollman, A.: *Pharmacology and Therapeutics,* Lea & Febiger, Phila., 1960, p. 482. 4. Winer, B. M.: *Circulation 22*:1074 (Dec.) 1960. 5. Martz, B. L.: *J. Indiana M. A. 52*:1779 (Oct.) 1959. 6. Fries, E. D.: *South M. J. 51*:1281 (Oct.) 1958. 7. Finnerty, F. A. and Buehholz, J. H.: *GP 17*:95 (Feb.) 1958. 8. Gill, R. J., *et al.: Am. Pract. & Digest Treat. 11*:1007 (Dec.) 1960. 9. Ford, R. V. and Nickell, J.: *Ant. Med. & Clin. Ther. 6*:461, 1959. 10. Brest, A. N. and Moyer, J. H.: *J. South Carolina M. A. 56*:171 (May) 1960. 11. Wilkins, R. W.: *Postgrad. Med. 26*:59 (July) 1959. 12. Gifford, R. W., Jr.: Read at the Hahnemann Symp. on Hypertension, Phila. Dec. 8 to 15, 1958. 13. Fries, E. D., *et al.: J.A.M.A. 166*:137 (Jan. 11) 1958.

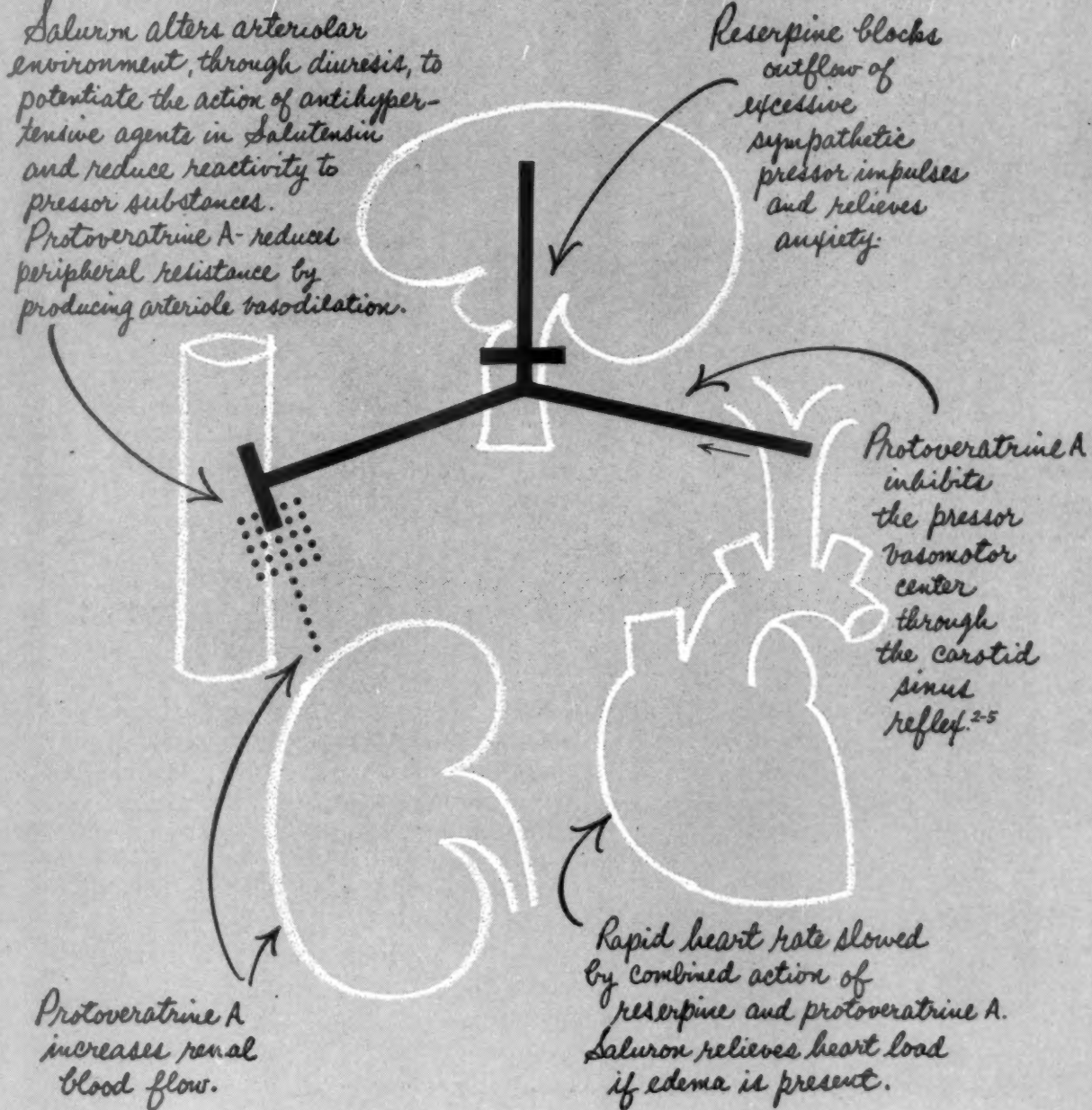
SALUTENSIN®

(hydroflumethiazide, reserpine, protoveratrine A—antihypertensive formulation)

BRISTOL LABORATORIES
Division of Bristol-Myers Co. / Syracuse, N.Y.

Also available—for edema, hypertension...when a thiazide alone is enough:
SALURON®(hydroflumethiazide) the 'dry-weight' diuretic with long-term benefits

Salutensin - What it does


Saluron alters arteriolar environment, through diuresis, to potentiate the action of antihypertensive agents in Salutensin and reduce reactivity to pressor substances.
Protoveratrine A- reduced peripheral resistance by producing arteriole vasodilation.
Reserpine blocks outflow of excessive sympathetic pressor impulses and relieves anxiety.
Protoveratrine A inhibits the pressor vasomotor center through the carotid sinus reflex.[2-5]
Protoveratrine A increases renal blood flow.
Rapid heart rate slowed by combined action of reserpine and protoveratrine A. Saluron relieves heart load if edema is present.

Lilly
QUALITY / RESEARCH / INTEGRITY

■ to improve
cardiac
function

CRYSTODIGIN®

permits
accurate dosage titration

Since initial digitalization and maintenance dosage must be carefully individualized, Crystodigin fulfills the important requirements of a preferred digitalis. Crystodigin is a crystalline-pure, uniformly potent single glycoside that is completely absorbed in the gastro-intestinal tract. With Crystodigin, the maximum therapeutic effect can be readily obtained by dosage titration in increments as small as 0.025 mg.

Available in scored tablets of 0.05 mg. (orange), 0.1 mg. (pink), 0.15 mg. (yellow), and 0.2 mg. (white); and in 1-cc. and 10-cc. ampoules, 0.2 mg. per cc.

Crystodigin® (crystalline digitoxin, Lilly)

170102

The American Journal of Cardiology

VOLUME VII MAY 1961 NUMBER 5

Clinical Studies

The Vectorcardiogram in Incomplete Left Bundle Branch Block*

CELESTINO SANCHEZ, M.D., THOMAS J. WALSH, M.D. *and* EDWARD MASSIE, M.D., F.A.C.C.

St. Louis, Missouri

WITHIN THE LAST fifteen years the electrocardiographic manifestations of incomplete left bundle branch block have been studied extensively and described by many investigators. At the present time, there exist more or less generally accepted criteria for the electrocardiographic diagnosis of incomplete left bundle branch block which have been derived not only from clinical study of this condition but also from observations reported by Sodi-Pallares and associates[1,2] in experimentally produced incomplete left bundle branch block in the canine heart.

The introduction of vectorcardiography has provided a new diagnostic technic which may yield further information about incomplete left bundle branch block as well as other cardiac abnormalities. Although several vectorcardiographic studies of incomplete left bundle branch block have already been reported,[1,3–5] they have disagreed somewhat as to the vectorcardiographic findings characteristic of incomplete left bundle branch block.

With the hope of promoting a better understanding and clearer delineation of the vectorcardiographic features of incomplete left bundle branch block, we are presenting in this paper an analysis of vectorcardiograms recorded from a group of patients with the electrocardiographic diagnosis of incomplete left bundle branch block.

MATERIAL AND METHODS

The study series consisted of vectorcardiograms recorded from twenty-one patients whose electrocardiograms were considered diagnostic of incomplete left bundle branch block. The criteria proposed by Sodi-Pallares[1] (with several modifications described later) were utilized in making the electrocardiographic diagnosis of incomplete left bundle branch block, but no attempt was made to distinguish between first and second degrees of incomplete left bundle branch block as has been done by Sodi-Pallares.

The electrocardiographic criteria used in this study for the diagnosis of incomplete left bundle branch block were as follows:

1. Slurring of the R wave in the left precordial leads or in lead I, involving the initial part and ascending limb of the R wave and occasionally the descending limb of this deflection.
2. QRS duration between 0.07 and 0.15 second.
3. Embryonic or preferably absent Q waves in the left precordial leads.
4. The presence of initial R waves in leads to the left of lead V_1. This criterion was added by us to exclude, insofar as possible, electrocardiograms of patients with anteroseptal myocardial infarction because this condition can also be associated with embryonic or absent Q waves in the left precordial leads.
5. Slight or marked left axis deviation of QRS (or ÂQRS).
6. Inverted, diphasic, or low or flattened T waves in the left precordial leads.

* From the Department of Medicine, Washington University Medical School and the Heart Station and Cardiovascular Laboratory, Barnes Hospital, St. Louis, Missouri.

TABLE I
Electrocardiograms of Patients with Incomplete Left Bundle Branch Block

Case No.	QRS Duration (sec.)	S in Lead V_1 + R in V_5 or V_6 (mm.)	ÂQRS (degrees)	ÂT (degrees)	Slurring of R in Leads I, V_5, V_6	Q in Leads V_5-V_6	T* in Lead V_5-V_6	Left Ventricular Enlargement by X-ray	Average Blood Pressure (mm. Hg)	QRS-T Angle (degrees) (frontal)
1	0.12	44	−60	+120	Yes	No	− −	No	150/80	180
2	0.08	44	0	180	No	No	+ −	...	...	180
3	0.08	41	−30	+60	Yes	No	+ +	No	160/110	90
4	0.10	47	+30	+60	Yes	No	+ −	...	150/110	30
5	0.12	15	−90	+90	Yes	No	− −	Yes	150/80	180
6	0.10	57	0	180	Yes	No	− −	Yes	130/80	180
7	0.08	31	+60	−60	Yes	No	+ +	...	...	120
8	0.10	58	+60	−120	Yes	No	− −	Yes	145/95	180
9	0.10	36	+30	−120	Yes	No	− −	Yes	100/60	150
10	0.10	44	+15	−165	Yes	No	− −	Yes	190/100	180
11	0.08	46	+60	+90	Yes	No	± ±	Yes	180/90	30
12	0.12	58	−45	+120	Yes	No	− −	Yes	120/75	165
13	0.08	30	+45	180	Slight	Embryonic	− −	...	150/40	135
14	0.08	18	−15	+165	Yes	No	− −	Yes	120/70	180
15	0.10	51	0	180	Yes	No	− −	...	...	180
16	0.11	25	0	+60	Yes	No	+ +	...	120/75	60
17	0.11	48	−30	+150	Yes	No	− −	Yes	140/80	180
18	0.12	23	+30	+120	Yes	No	± −	...	...	90
19	0.12	33	+20	+150	Yes	No	− −	Yes	140/80	130
20	0.08	44	+60	+60	Slight	No	+ +	No	160/95	0
21	0.12	21	−60	+120	Yes	No	− −	No	160/100	180

* Symbols in this column are as follows: − = negative T wave; + = positive T wave; and ± = diphasic T wave.

The electrocardiograms of patients included in this study series were also reviewed to determine whether they fulfilled the criterion for the diagnosis of left ventricular hypertrophy of an S in V_1 + R in V_5 or V_6 greater than 35 mm. For simplicity, no additional criteria for the diagnosis of left ventricular hypertrophy were utilized.

The vectorcardiograms were displayed on the Sanborn Viso-Scope in the three standard planes as follows: (1) horizontal; (2) left sagittal (which was reversed and read as a right sagittal for the sake of convenience); and (3) frontal. The vectorcardiograms were recorded with the corrected lead system as described by Frank.[6] In determining the vectorcardiographic QRSsÊ-TsÊ angle, the method used was that of Helm and Fowler.[7] The orientations of the different vectors in the planar projections of the vectorcardiogram were expressed in terms of the reference frame which is formed by a transverse coordinate axis extending from 0° on the left of the reference frame (the observer's right) to 180° on the right (the observer's left) and dividing the reference frame into an upper half marked off in −30° segments in a counterclockwise direction and a lower half in +30° segments in a clockwise direction from left to right. Thus, 0° in the reference frame is situated to the left (the observer's right) in the frontal and horizontal planes and anteriorly in the right sagittal plane; +90° is located inferiorly in the frontal and sagittal planes and anteriorly in the horizontal plane.

Case Material: Most of the patients in the study series had routine roentgenograms of the chest which were reviewed to determine the presence or absence of left ventricular hypertrophy (or enlargement). The average of many blood pressure readings was also determined for each patient with the exception of four patients whose blood pressures were not recorded. Twelve of the subjects were men and nine women. The ages of these patients varied between fifty and eighty-eight years and the clinical diagnosis in each case was arteriosclerotic heart disease and/or hypertensive cardiovascular disease.

RESULTS

Table I summarizes the electrocardiographic and clinical findings of twenty-one patients whose electrocardiograms were considered to be compatible with the diagnosis of incomplete left bundle branch block.

Clinical Findings: In six cases in the study series the average diastolic blood pressures ranged from 95 to 100 mm. Hg; the remaining eleven patients had average diastolic pressures within normal limits. In ten cases the average systolic blood pressure exceeded 140 mm. Hg; it ranged between 100 and 140 mm. in seven subjects. No blood pressure recording was available in the remaining four cases. The roentgenograms of the chest in ten of the twenty-one patients demonstrated radiologic evidence of left ventricular enlargement; the x-rays of the chest in four of the cases showed no evidence of this abnormality. In the remaining seven patients no roentgenograms of the chest were available for examination.

TABLE II
Vectorcardiograms of Patients with Incomplete Left Bundle Branch Block

Case No.	Plane *	QRSsÊ Loop Initial Deflection†	QRSsÊ Loop Inscription‡	Conduction Delay Localization	QRSsÊ-TsÊ Angle (degrees)	QRSsÊ Loop Main Vector (degrees)	S-T Vector Orientation†
1	H	PLI	CCW/CW	Generalized	180	−50	RA
	F		CCW			−20	
	S		CW			−170	
2	H	ALI	CCW/CW	0	180	−25	...
	F		CCW			+5	
	S		CW			+160	
3	H	ALI	CW	Afferent limb	180	−40	RAS
	F		CCW			−15	
	S		CW			−165	
4	H	ALI	CCW/CW	Initial and generalized	180	−30	RS
	F		CCW			0	
	S		CW			+175	
5	H	PLI	CCW/CW	Initial and generalized	180	−35	RA
	F		CCW			−30	
	S		CW			−135	
6	H	ALI	CCW/CW	Generalized	180	−20	RA
	F		CCW			0	
	S		CW			180	
7	H	ALI	CCW	Initial and generalized	180	−15	RS
	F		CCW			+15	
	S		CW			+135	
8	H	ALI	CCW/CW	Afferent limb	180	−55	R
	F		CW			+40	
	S		CW/CCW			+155	
9	H	PLI	CCW	Afferent limb	180	−50	RA
	F		CW/CCW			+35	
	S		CW			+160	
10	H	ALI	CCW/CW/CCW	Generalized	180	−50	RS
	F		CCW			+25	
	S		CW			+155	
11	H	ALI	CCW	Initial and afferent limb	135	−20	R
	F		CW/CCW			+30	
	S		CW			+130	
12	H	ALI	CCW/CW	Initial and generalized	180	−55	RA
	F		CCW			−10	
	S		CW			180	
13	H	ALS	CCW/CW	Initial and efferent limb	180	−60	RS
	F		CCW/CW			+45	
	S		CCW			+140	
14	H	ALS	CCW	Generalized	180	−60	R
	F		CW/CCW			0	
	S		CCW			180	
15	H	ALI	CCW/CW	Initial	180	−60	...
	F		CCW			+12	
	S		CW/CCW			+160	
16	H	ALI	CCW/CW	0	150	−50	...
	F		CCW			+10	
	S		CW			+170	
17	H	ALI	CCW/CW	Initial and terminal	180	−35	RAS
	F		CCW			+45	
	S		CW			+120	
18	H	ALI	CCW/CW	0	180	−65	RPS
	F		CW/CCW			+30	
	S		CW/CCW			+170	

TABLE II *Continued next page*

TABLE II *Continued*

Case No.	Plane*	QRSsÊ Loop Initial Deflecton†	QRSsÊ Loop Inscription‡	Conduction Delay Localization	QRSsÊ-TsÊ Angle (degrees)	QRSsÊ Loop Main Vector (degrees)	S-T Vector Orientation†
19	H	ALI	CCW/CW	Initial and generalized	180	−59	RAS
	F		CCW			+10	
	S		CW			+170	
20	H	LPI	CCW/CW	Efferent limb	65	−20	...
	F		CCW			+30	
	S		CW/CCW			+135	
21	H	ALI	CCW/CW	Initial	180	−35	RPI
	F		CCW			−25	
	S		CW			−140	

* Abbreviations in this column are as follows: H = horizontal; F = frontal; and S = sagittal.
† Abbreviations are as follows: A = anterior; S = superior; P = posterior; I = inferior; L = left; and R = right.
‡ CW = clockwise and CCW = counterclockwise.

Electrocardiograms: The QRS durations in the twenty-one electrocardiograms varied between 0.08 and 0.12 second with an average of 0.10 second. The sum of S in V_1 and R in V_5 or V_6 exceeded 35 mm. in thirteen of the twenty-one electrocardiograms and averaged 39 mm. for the entire group of twenty-one tracings. ÂQRS varied in orientation between −90° and +60° with an average of about +5°. Q waves were absent in leads V_5 and/or V_6 in all cases and there was slurring on the upstrokes of the R waves in these leads in all but

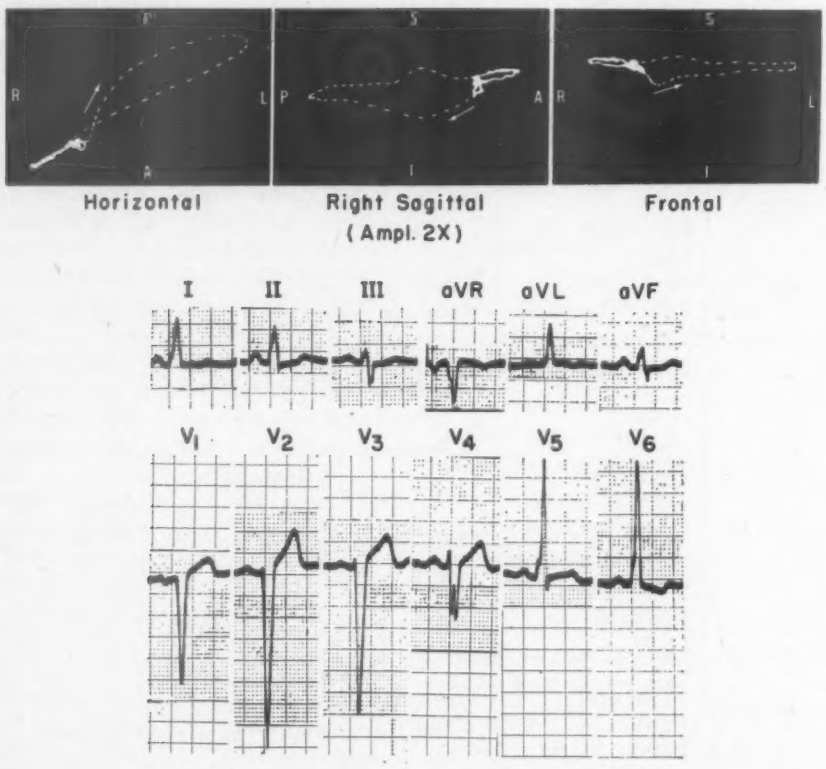


FIG. 1. Case 4. Vectorcardiogram and electrocardiogram. Note the leftward and anterior initial deflection and subsequent clockwise inscription of the horizontal QRS loop. The conduction delay is best displayed in the early portion of the efferent limb of the frontal QRS loop.

one electrocardiogram. The T waves in leads V_5 and V_6 were abnormal in all but four records. The frontal plane angle subtended by ÂQRS and ÂT (QRS-T angle) exceeded 60° in all but four electrocardiograms, the average width of the QRS-T angle for the twenty-one electrocardiograms being about 135°.

VECTORCARDIOGRAMS

Initial Deflection of QRS Loop: In Table II are presented the characteristic features of the vectorcardiograms of the twenty-one patients whose electrocardiograms were interpreted as incomplete left bundle branch block. In all of the vectorcardiograms the normal initial deflection of the QRSsÊ loop to the right and anterior was absent. Instead, in fifteen of the twenty-one cases the initial deflection of the QRSsÊ loop was oriented anteriorly, to the left and inferiorly. In four other vectorcardiograms the initial deflection was directed to the left, posteriorly and inferiorly, and in the last two cases it was inscribed anteriorly, to the left and superiorly (Figs. 1, 2, 3).

Inscription of QRS Loop: In the *horizontal plane* of fifteen vectorcardiograms, the QRSsÊ loop described a figure of eight configuration with its proximal portion having a counterclockwise (CCW) inscription and its distal portion a clockwise (CW) direction of inscription (i.e., the loop was CCW/CW inscribed). The QRSsÊ loop in the horizontal projection of four other vectorcardiograms was entirely counterclockwise inscribed. Only one horizontal QRS loop in this group of cases had a totally clockwise inscription. The remaining vectorcardiogram showed a bizarre configuration of the QRSsÊ loop in the horizontal projection resembling a double figure of eight configuration, the proximal, middle and distal components of which were counterclockwise, clockwise and counterclockwise inscribed, respectively.

In fourteen vectorcardiograms the *frontal* QRS loop had a counterclockwise inscription and in one case, a clockwise inscription. In the remaining five vectorcardiograms the frontal QRS loop displayed a figure of eight configura-

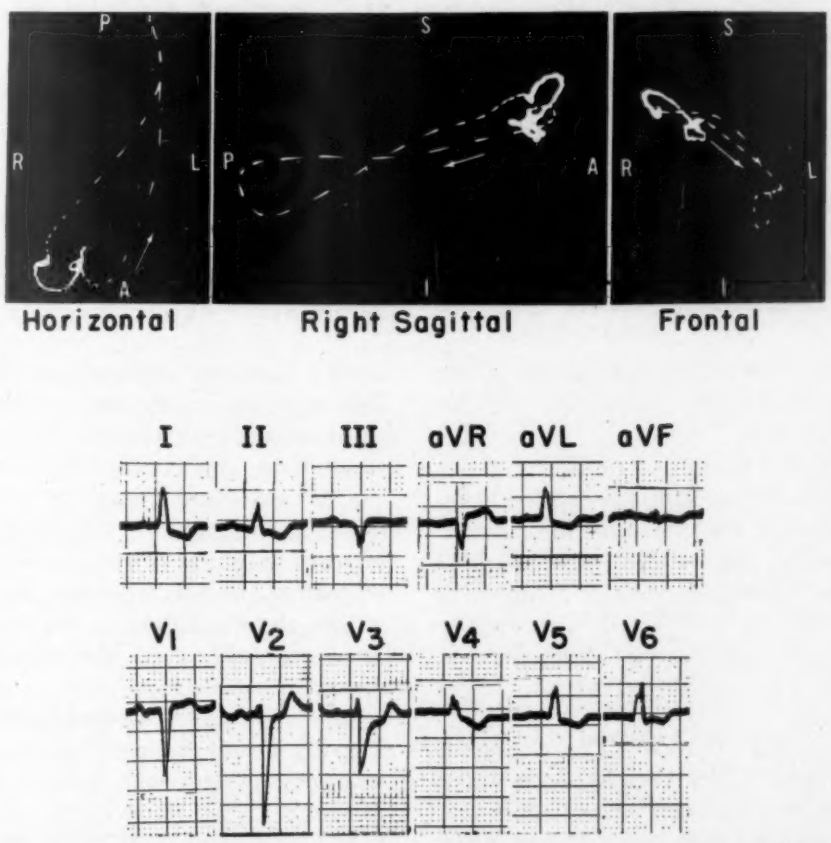


FIG. 2. Case 18. Vectorcardiogram and electrocardiogram. The QRSsÊ loop is written initially to the left, anteriorly and inferiorly. Note the displacement of the terminus of the QRSsÊ loop to the right and superiorly, indicating a similarly directed S-T vector.

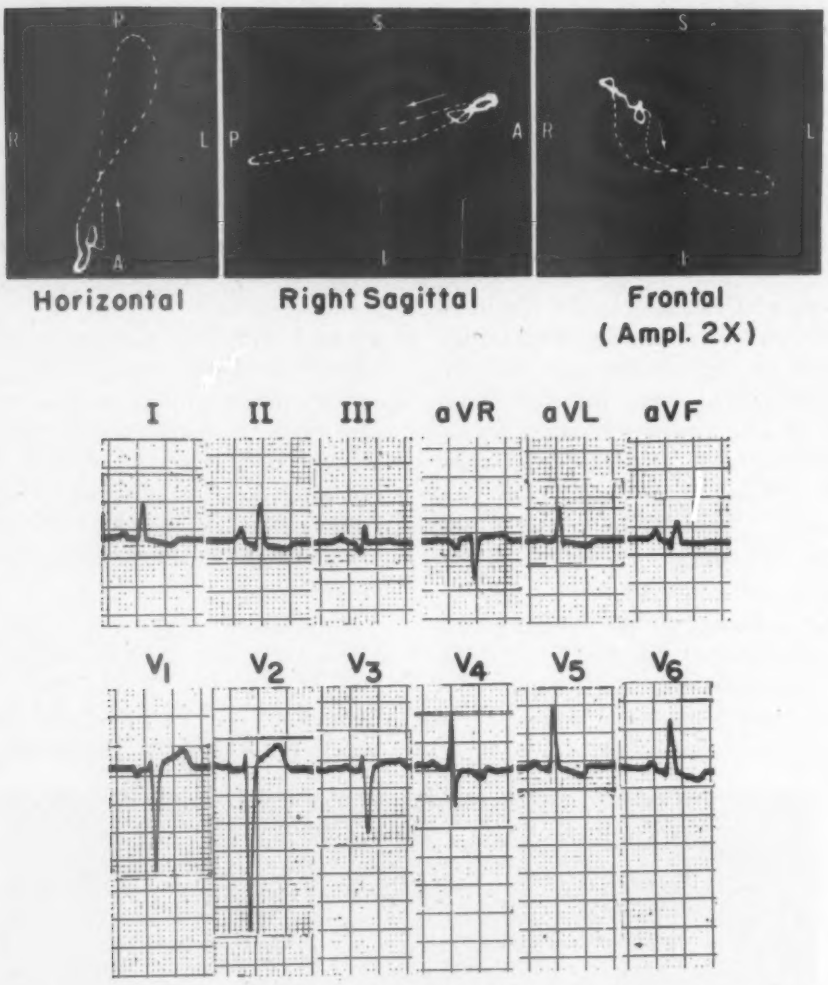


FIG. 3. Case 13. Vectorcardiogram and electrocardiogram. The vectorcardiogram presents the typical features of incomplete left bundle branch block. In lead I of the accompanying electrocardiogram, Q waves cannot be identified but embryonic Q waves are recorded in leads V_5 and V_6.

tion, with a CW/CCW inscription in four of the records and a CCW/CW inscription in the fifth vectorcardiogram.

In the right *sagittal* projection of fifteen of the twenty-one vectorcardiograms, the QRSsÊ loop showed a clockwise direction of inscription. In four vectorcardiograms the right sagittal projection of the QRSsÊ loop had a figure of eight contour with a CW/CCW inscription. The last two vectorcardiograms demonstrated a counterclockwise inscription of the right sagittal QRS loop.

Orientation of QRS Vectors: The maximal mean instantaneous QRS vectors determined from the horizontal QRS loops of the twenty-one vectorcardiograms were oriented between $-65°$ and $-15°$, with an average of $-42°$. The orientation of the corresponding vector of the frontal QRS loop varied between $-30°$ and $+45°$, with an average orientation of $+10°$. The maximal mean instantaneous vector of the right sagittal projection of the QRSsÊ loop ranged in orientation between $+120°$ and $-135°$ with an average of $+167°$. Figure 4 shows the ranges of variation (shaded areas) of the maximal mean instantaneous planar vectors of the QRSsÊ loop, the straight arrows within the shaded areas representing the average orientations of the mean instantaneous vectors.

Conduction delay, as evidenced in the QRSsÊ loop by closely spaced time dashes, was present to a varying degree in most of the vectorcardiograms. There were three exceptions to this rule. In two of these three vectorcardiograms, the QRSsÊ loop showed no evidence of conduction delay while in the remaining vectorcardiogram it was not possible to establish or exclude

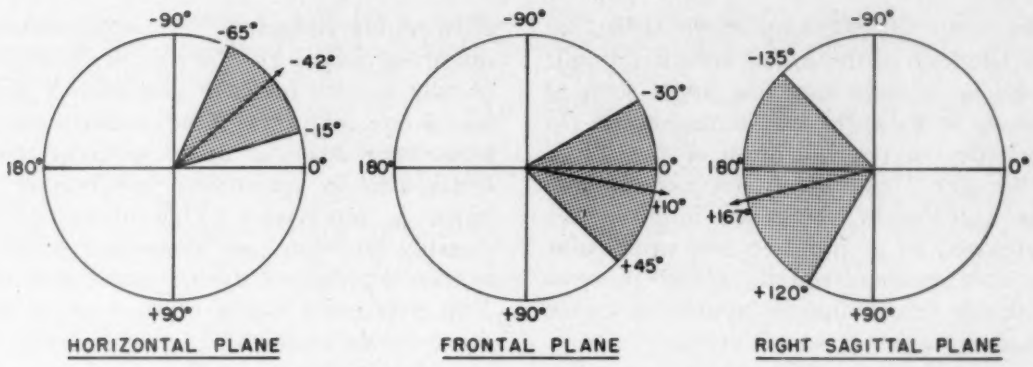


FIG. 4. The shaded segments of the above reference frames represent the range of variation of the maximal mean instantaneous vectors of the QRSsÊ loop in incomplete left bundle branch block while the arrows indicate the average orientations of these vectors.

the presence of conduction delay for technical reasons. In the eighteen vectorcardiograms showing conduction delay, the slowing was observed often to involve more than one portion of the same QRSsÊ loop, the initial deflection and afferent limb of the loop being the most common sites of conduction delay. Not infrequently the entire QRSsÊ loop in each projection of the vectorcardiogram displayed the closely spaced time dashes indicative of conduction delay.

S-T Vector: In fifteen of the twenty-one vectorcardiograms studied, the QRSsÊ loop remained open after its inscription, indicating the presence of an S-T vector which was directed invariably to the right and anteriorly and/or superiorly. Only in one case was the S-T vector oriented to the right, posteriorly and inferiorly. In the five remaining vectorcardiograms it was not possible to detect an S-T vector.

Spatial QRS-T Angle: In eighteen of the twenty-one vectorcardiograms, the QRSsÊ-TsÊ angle* was 180°. In the three remaining vectorcardiograms the QRSsÊ-TsÊ angles were 135°, 150° and 65° respectively.

QRS Vector Magnitude: Although no attempt was made to determine the absolute magnitudes of the maximal mean instantaneous vectors of the planar QRS loops of the vectorcardiogram, it was apparent that the magnitudes of the maximal mean instanteous vectors of the horizontal and frontal QRS loops of the vectorcardiograms showing incomplete left bundle branch block were, with but one exception, larger than normal.

COMMENTS

In a vectorcardiographic study series of patients with chronic coronary heart disease and electrocardiographic evidence of either right bundle branch block or left bundle branch block (complete or incomplete) reported by Cabrera and associates,[4] there were seventeen patients with electrocardiographic incomplete left bundle branch block. In four of these seventeen patients, the vectorcardiograms revealed horizontal and frontal QRS loops differing from those considered diagnostic of complete left bundle branch block only in that they exhibited no evidence of conduction delay. These four vectorcardiograms Cabrera et al. interpreted as being compatible with incomplete left bundle branch block. In the remaining thirteen of the seventeen cases of electrocardiographic incomplete left bundle branch block, most of the vectorcardiograms had QRS loops with diminutive anterior and rightward (only rarely leftward) initial deflections; conduction delay in the centrifugal limbs of the QRS loops was only rarely observed. All of the cases of electrocardiographic incomplete left bundle branch block were diagnosed clinically as having chronic coronary heart disease, this being one of the determining factors in the selection in the cases for their study; therefore, Cabrera et al. hypothesized that the diminutive initial deflections of the QRSsÊ loop in these thirteen cases without the typical vectorcardiographic findings of incomplete left bundle branch block might have two alternative mechanisms other than incomplete left bundle branch block, namely: (1) the small initial

* QRSsÊ-TsÊ angle: the spatial angle subtended by the long axes or maximal mean instantaneous spatial vectors of the QRSsÊ and TsÊ loops, as computed by the method of Helm and Fowler.[7] In our laboratory a QRSsÊ-TsÊ angle of 45° or less is considered normal.

deflection of the QRSsÊ loop might reflect an intrinsic reduction of the initial vectors brought about by loss of some muscular units such as might occur in subendocardial fibrosis, or (2) it might reflect a neutralization of the initial vectors brought about by an increase of synchronous antagonistic forces as might result from hypertrophy of the free left ventricular wall, the increased voltage of the high posterolateral vectors being opposed to and for a time contemporary with left septal vectors.

Our series of cases of electrocardiographic incomplete left bundle branch block is comparable to the series of Cabrera and associates in that all of the patients in our study group were diagnosed clinically as having arteriosclerosis and/or hypertensive cardiovascular disease and all had electrocardiographic incomplete left bundle branch block. However, the vectorcardiographic findings in our series of twenty-one cases of electrocardiographic incomplete left branch block differed in several important respects with the findings in the thirteen patients whose vectorcardiograms Cabrera et al. did not consider typical of incomplete left bundle branch block. First, without exception, every vectorcardiogram in our series showed a QRSsÊ loop which was inscribed initially to the left, usually anteriorly and inferiorly. Second, in eighteen of the twenty-one vectorcardiograms the QRSsÊ loop displayed conduction delay in one or more portions of the loop in every planar projection.

The mechanism of the leftward initial deflection of the QRSsÊ loop of the vectorcardiogram and of the initial slurred upstroke of the R wave in leads I, aVL and V_6 of the electrocardiogram in incomplete left bundle branch block is explained by Sodi-Pallares and associates[1,2] in the following way: "the functional capacity of the left bundle branch is to a varying degree affected so that the excitation impulse, though not blocked, is conducted down the left bundle branch at a slower rate than normal. Thus the normal time lag of right septal activation behind onset of excitation on the left septal surface tends to be abolished with the result that the initial forces due to left to right septal depolarization are opposed and, in part at least, neutralized; or in more severe degrees of incomplete left bundle branch block the delayed conduction may be such that while the left bundle branch activates some of the muscle mass of the left septum the remainder receives the excitation impulse trans septally from the right bundle branch." This explanation of the abnormal initial QRS forces in incomplete left bundle branch block is certainly a well reasoned one; however, the mechanism of the frequently observed figure of eight horizontal QRS loop in incomplete left bundle branch block is not clear. This abnormality may possibly be related to anomalous activation of at least a portion of the left ventricular free wall. This hypothesis would be in keeping with the observations by us and by other investigators, notably Gardberg and Rosen,[5] that in patients with intermittent incomplete left bundle branch block, with onset of the conduction defect there is an almost immediate increase in the QRS voltage, particularly in right precordial leads. This would suggest either that activation of the left ventricular free wall may take place in a somewhat aberrant fashion, thereby producing electrical forces of greater magnitude, or, alternatively, that the increased QRS voltage in incomplete left bundle branch block may reflect unopposed activation of some portions of the left ventricular free wall as the result of delayed impulse conduction down the left bundle branch.

Summary

Twenty-one cases with electrocardiographic findings of incomplete left bundle branch block unaccompanied by findings suggestive of anteroseptal infarction were studied vectorcardiographically. The vectorcardiographic findings correlated closely with the electrocardiographic abnormalities in these cases in that the QRSsÊ loop was invariably written to the left and usually anteriorly and inferiorly, and there was often conduction delay in the initial deflection of the loop or, on occasions, in other portions of the loop. These findings would be the vectorcardiographic counterpart of the slurred initial upstroke of the R wave in leads I, aVL and V_6 of the electrocardiogram. The characteristic figure of eight configuration and posterior rotation of the QRSsÊ loop in the horizontal projection were also of diagnostic value in the recognition of the pattern of incomplete left bundle branch block.

References

1. Sodi-Pallares, D. and Calder, R. M. New Bases of Electrocardiography, p. 289. St. Louis, 1956. C. V. Mosby Co.
2. Rodriguez, M. I. and Sodi-Pallares, D. The mechanism of complete and incomplete bundle

branch block. *Am. Heart J.*, 44: 715, 1952.
3. GRISHMAN, A. and SCHERLIS, L. Spatial Vectorcardiography, p. 90. Philadelphia, 1952. W. B. Saunders Co.
4. CABRERA, E., GARCIA-FONT, R., GAXIOLA, A., and PILEGGI, F. The vectorcardiogram of ventricular activation in chronic coronary heart disease. *Am. Heart J.*, 55: 557, 1958.
5. GARDBERG, M. and ROSEN, I. L. The electrocardiogram and vectorcardiogram in various degrees of left bundle branch block. *Am. J. Cardiol.*, 1: 592, 1958.
6. FRANK, E. An accurate clinically practical system for spatial vectorcardiography. *Circulation*, 13: 736, 1956.
7. HELM, R. A. and FOWLER, N. O., JR. A simplified method for determining the angle between two spatial vectors. *Am. Heart J.*, 45: 835, 1953.

The Vectorcardiogram in Left Bundle Branch Block*

RAFAEL LUNA,† M.D. *and* ALBERT JACKSON, M.D.

Kansas City, Kansas Wadsworth, Kansas

THERE IS EVIDENCE that the vectorcardiographic approach is helpful in the study of left bundle branch block. Some facts, such as the appearance of the Q wave in lead V_6, the relationship between the plateau and the duration of the QRS loop, the behavior of the T loop in primary and secondary changes and the correlation with known steps of ventricular activation still need to be elucidated. This is the purpose of this paper.

MATERIAL AND METHODS

The vectorcardiograms of thirty patients were studied. These vectorcardiograms had QRS loops with a duration of more than 100 milliseconds, clockwise rotation in the horizontal plane and the long axis deviated posteriorly and to the left. These are, generally speaking, the criteria for left bundle branch block. Twenty-nine of the thirty patients were men because a great part of this work was done in a Veterans Administration Hospital. Their ages varied from twenty-four to eighty years. The clinical histories of these patients were studied and routine twelve lead electrocardiograms were taken. Special attention was paid to their histories and every effort was made to exclude patients with myocardial infarction.

Grishman's cube reference system was used.[1] In order to have a good visualization of the details near the E point, the gain was at times increased twentyfold. A Sanborn vectorcardiograph model 185, a Hart vectorcardiograph model PV3 and an oscilloscope matched with two Sanborn preamplifiers model 55, with a special switch box, were used. The vectorcardiograms were interrupted 400 times per second by intensity modulation. They were photographed either with a Polaroid camera or with a 35 mm. Exacta camera. The Q, R and ST-T loops of the vectorcardiogram were studied as separate entities. The time, direction, sense and position of each loop were studied in each plane. The ventricular gradient was obtained in an attempt to establish whether the T changes were primary or secondary and to compare them with the position, rotation and speed of the T loop.

RESULTS

The main loop of these vectorcardiograms was divided into two parts; the Q loop and the R loop. No S loop was identified in this study. Of the thirty cases studied, five had a duration of the QRS of from 100 to 114.5 milliseconds with an average duration of 106 milliseconds and twenty-five had a duration of from 122.5 to 200 milliseconds with an average duration of 153 milliseconds. Of the five cases with a duration of 100 to 114.5 milliseconds, four had Q loops.

Q LOOP

The small deflection directed to the right at the beginning of the QRS loop, in the frontal and horizontal planes, was called the Q loop. In the sagittal plane it could be found only by an integration from the two other planes. The limit of this loop has been arbitrarily set at the point where it crosses the anteroposterior or vertical axis in the horizontal and frontal planes, respectively. In order to better visualize this small loop, close-ups of the E point were taken. The Q loop was found only in six vectorcardiograms. In the horizontal plane its long axis was between +90° and +130°. This initial deflection directed to the right has already been noted on vectorcardiographic tracings or experimentally by others[2,3] (Fig. 1).

R LOOP

The R loop showed clockwise rotation in the horizontal plane and a posterior and leftward direction in all cases (Fig. 2). In the sagittal

* From the Cardiovascular Laboratories, Kansas University Medical Center, Kansas City, Kansas; and the Veterans Administration Hospital, Veterans Administration Consolidated Center, Wadsworth, Kansas.

† Present address: Hospital do Servidor da Guanabara, Rio de Janeiro, Brazil.

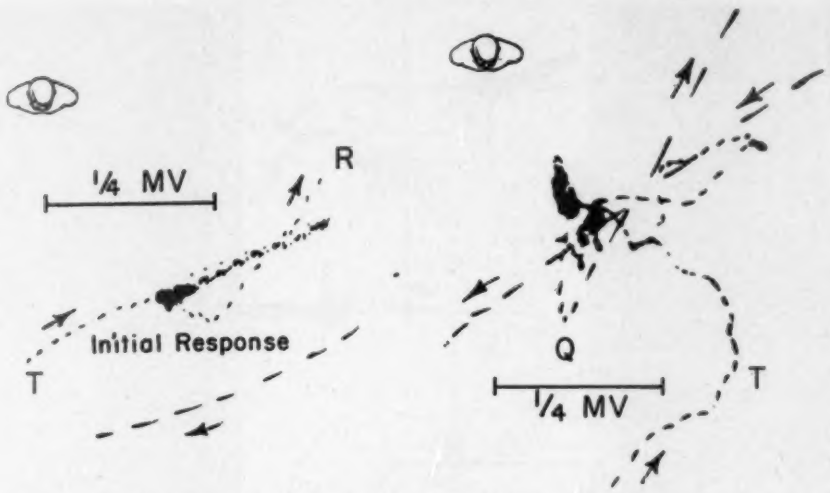


FIG. 1. On the left side the initial part of the QRS loop is formed by the initial component; this is the type usually seen in left bundle branch block. On the right, the initial part of the QRS loop is formed by the Q loop, rarely seen in left bundle branch block. Figure retouched.

plane the rotation was clockwise with two exceptions, in which cases the loop had a figure of eight configuration (Fig. 3). In the frontal plane the rotation was always counterclockwise. These rotations of the R loop seem to be constant in left bundle branch block. In order to obtain more details we divided the R loop into an initial component, a centrifugal limb, a plateau and a centripetal limb. The initial component of the R loop must not be confused with the Q loop, the first being directed anteriorly and to the left, the latter anteriorly and to the right (Fig. 1). Five of the twenty-four vectorcardiograms without a Q loop had no initial component even on twenty-fold amplification. There was no correlation between the duration of the R loop and the presence or absence of the initial component. The initial component was a very common and characteristic finding in left bundle branch block. The duration of the initial component averaged eighteen milliseconds. The centrifugal limb was always situated posteriorly and inferiorly, relative to the centripetal limb. In five cases with a duration from 100 to 114.5 milliseconds, four had no plateau. Of the twenty-five cases with a QRS duration greater than 122.5 milliseconds, seven had no plateau. The total duration of the R loop averaged 143 milliseconds, with a range of from 104 to 107 milliseconds. In five cases in which the QRS loop was less than 120 milliseconds in duration, the R loop ranged between 88 and 104 milliseconds with an average of 96.5 milliseconds. The duration of the plateau had a constant relationship to the duration of the QRS loop; the longer the duration of the QRS loop, the longer that of the plateau and more frequent its occurrence (Fig. 4).

The direction of the long axis of the R loop in the horizontal plane varied from $-70°$ to $-10°$, the average being $-39°$. In the right sagittal plane the long axis was directed straight posteriorly in 180° and in the frontal

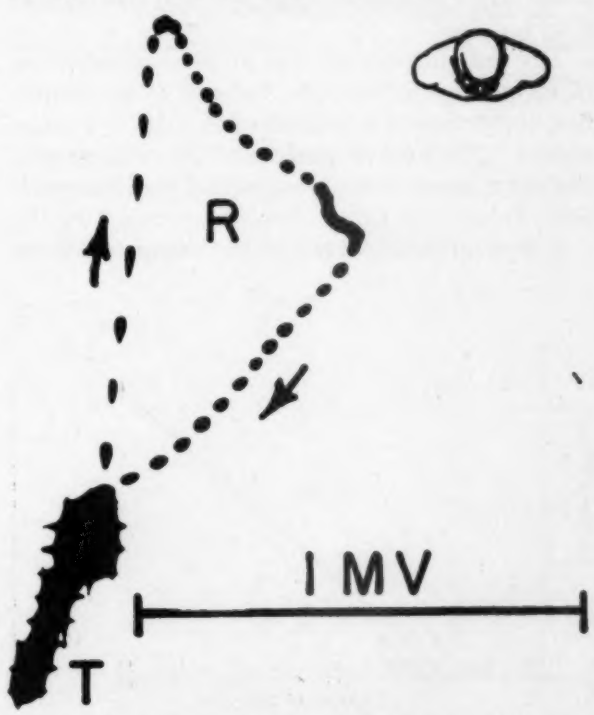


FIG. 2. R loop in the horizontal plane. Note the clear separation between the centrifugal limb, plateau and centripetal limb.

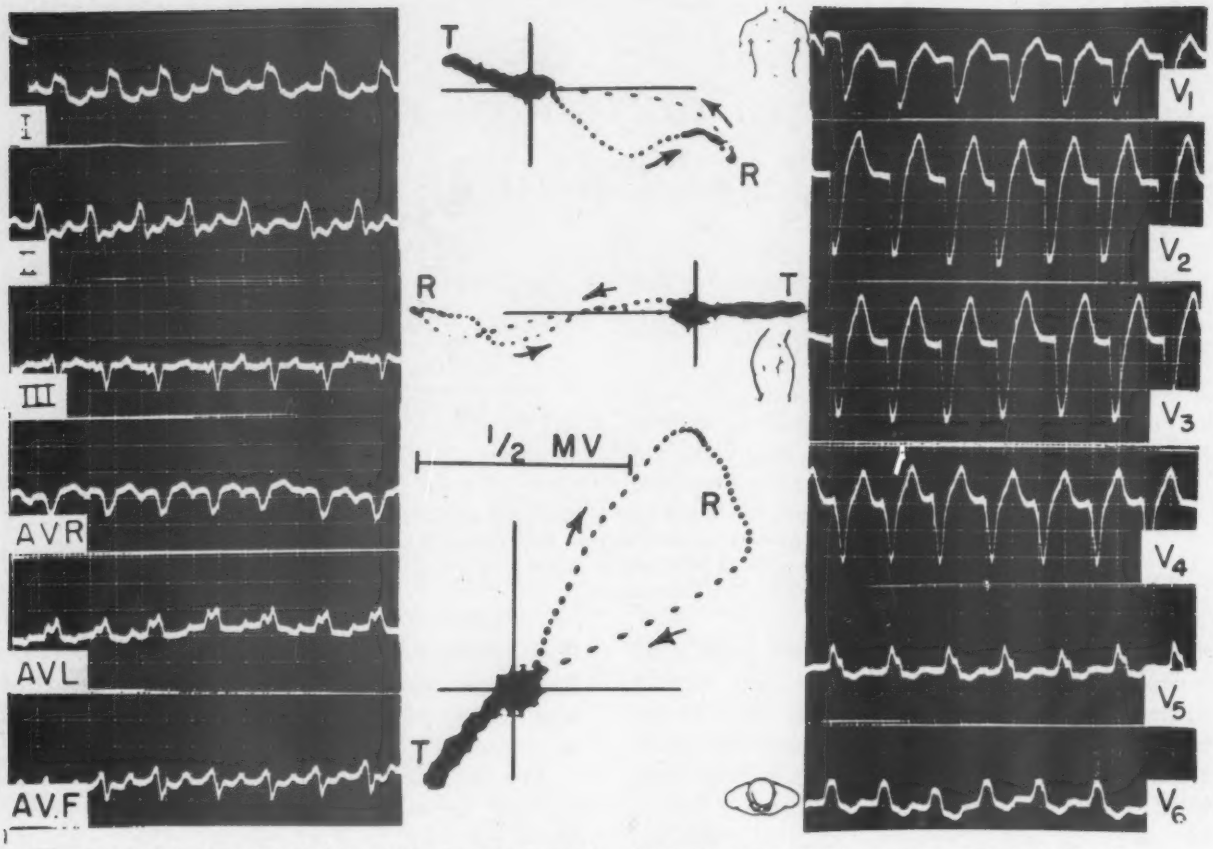


Fig. 3. Left bundle branch block (linear and vectorial). Note the figure of eight rotation in the sagittal plane.

plane it was directed straight to the left at 0° (Figs. 3, 5).

The centrifugal limb had an average duration of forty-five milliseconds, varying from twenty-five to seventy-five milliseconds. In five cases with a QRS loop of less than 120 milliseconds, the centrifugal limb averaged 32.5 milliseconds (Fig. 2).

The centripetal limb had an average duration of sixty-three milliseconds, varying from 42.5 to 75.0 milliseconds. In five cases with a QRS loop of less than 120 milliseconds, the centripetal limb averaged sixty milliseconds (Fig. 2).

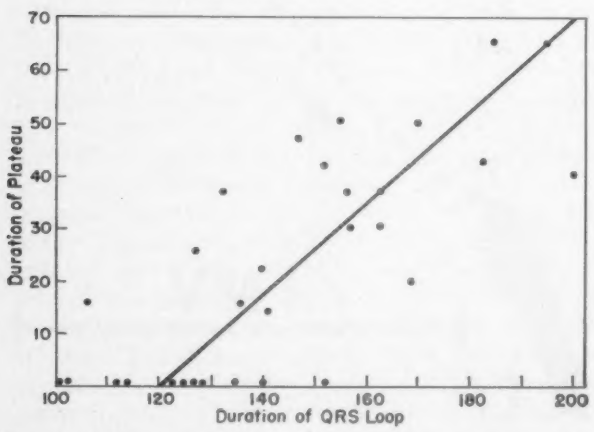


Fig. 4. Graph showing the relation between the duration of the QRS loop and the duration of the plateau. Note the straight line.

The duration of the plateau averaged thirty-eight milliseconds, varying from fifteen to sixty-five milliseconds. It represented twenty-six per cent of the R loop, the centrifugal limb represented 31 per cent and the centripetal limb 43 per cent, respectively (Fig. 6).

ST-T LOOP

The J point was deviated to the right and anteriorly due to early repolarization of the right ventricle; this would suggest that there is an opposition between the R loop and the displacement of the J point, caused by an asynchronism in ventricular repolarization, the right starting before the left[2] (Fig. 7).

The T loop was also opposite to the QRS loop. The shape of the T loop varied from a narrow, closed loop to a short and more open circle. In the horizontal plane its position was between +170° and +110° with an average of +134°. In the right sagittal plane the T

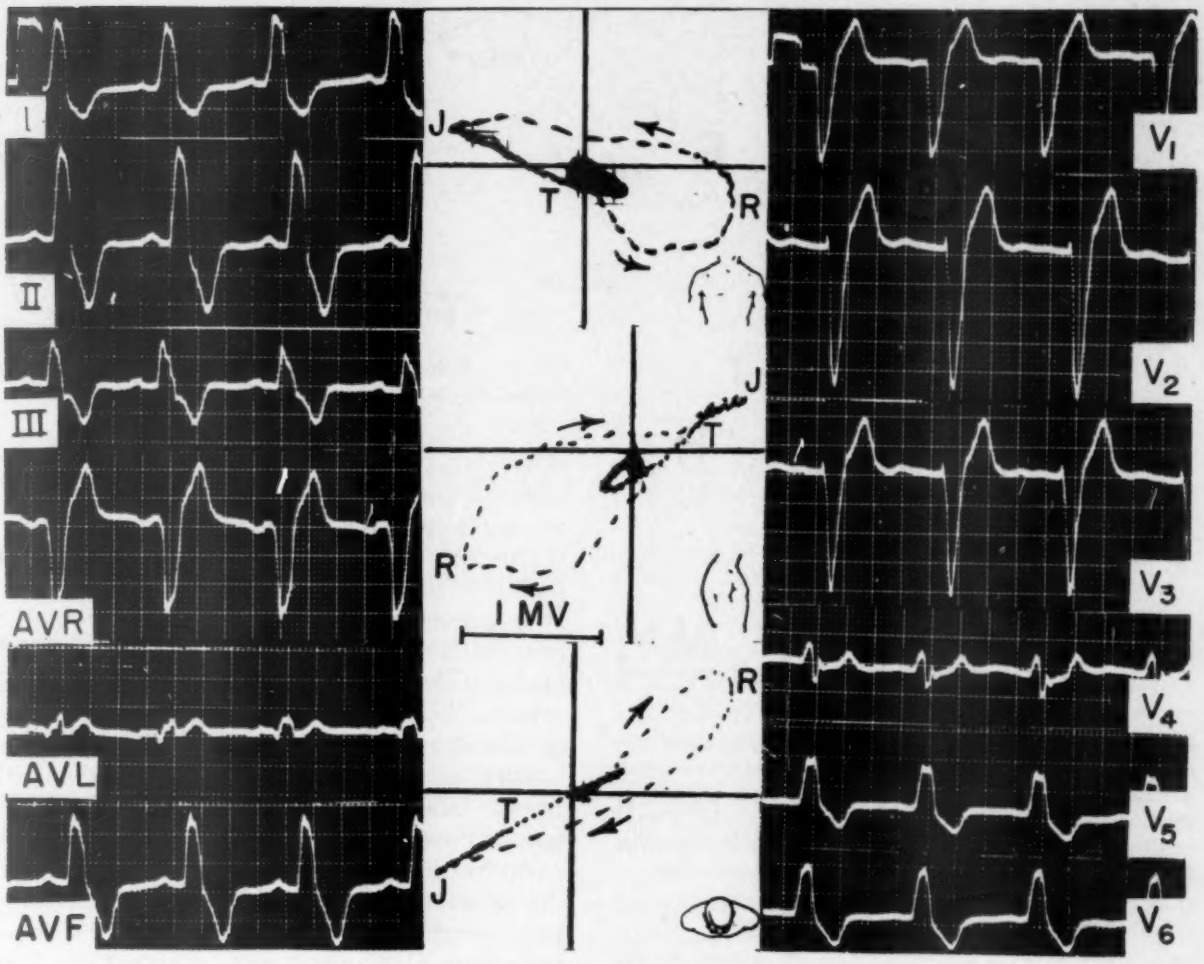


FIG. 5. Left bundle branch block (linear and vectorial). Note the opposition between the J point and the R loop in all three planes.

loop was at 0° and in the frontal plane it was at 180°. The direction of the inscription of this loop was generally counterclockwise and closed in the horizontal plane, clockwise in the right sagittal plane and counterclockwise in the frontal plane. Approximately one third of the loops in each plane did not follow this general orientation.

Of our thirty cases, twenty-two had no important torsion on the T loop. Of the other eight cases, three had a definitely twisted T loop. The ventricular gradient showed predominantly secondary T wave changes. It is possible that primary T wave changes have been obliterated by intense secondary changes of the left bundle branch block. We believe, as has been thought by others,[4] that we could not correlate our T loops with the ventricular gradient (Figs. 8, 9).

Another interesting finding was the presence, in many cases, of a slow centrifugal limb of the T loop and of a fast centripetal limb. In our three cases with torsion of the T loop the speed of the centrifugal and centripetal limbs was the same, a distinctly abnormal clinical finding.

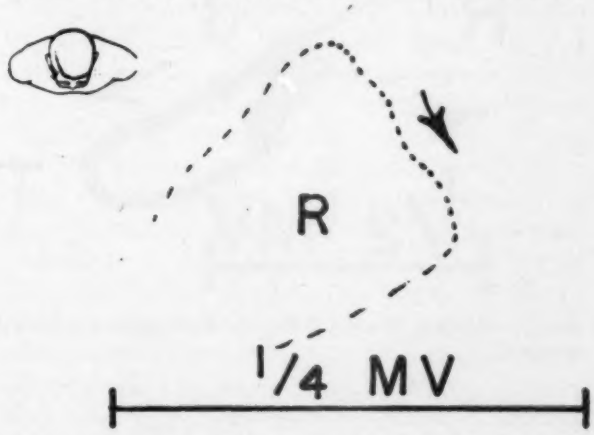


FIG. 6. Detail of the plateau in the horizontal plane. Its duration is in direct relation with the duration of the QRS loop.

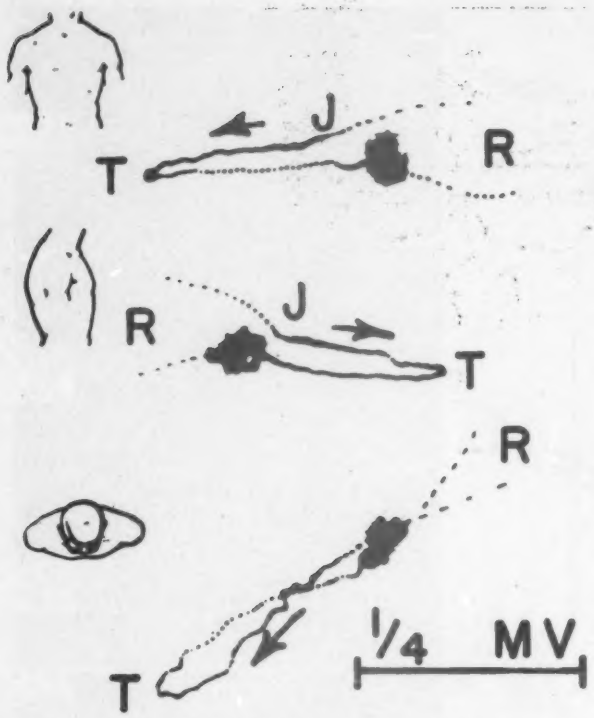


FIG. 7. The J point is deviated to the right, superiorly and anteriorly, as usually happens in left bundle branch block. The T loop has the centrifugal limb delayed in relation to the centripetal limb. Note that the T loop in the frontal and sagittal planes has the same rotation as the QRS loop.

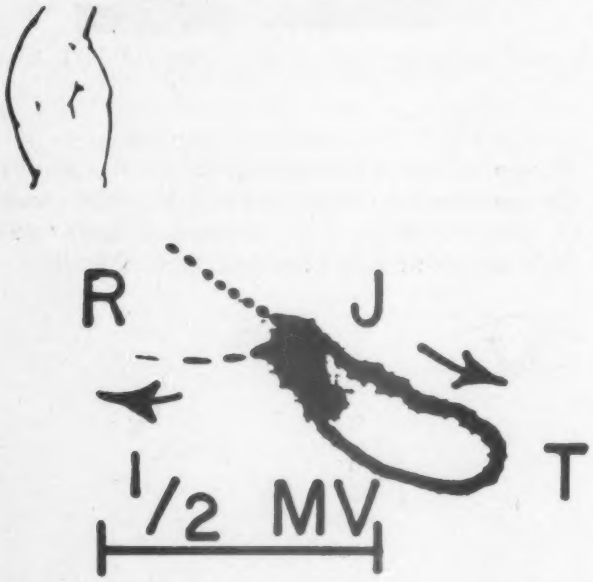


FIG. 8. Similar speed of T loop limbs suggests a primary change.

COMMENTS

Vectorcardiography permits the study of the electrical phenomena of the heart and correlation with already known steps of ventricular activation. If we advocate the dipole theory and use the activated regions as a "sink" in relation to the unactivated regions as a "source," it can very easily be shown that the vector is pointing from the "sink" to the "source." It is important to have this vector orientation in mind because it provides the only reasonable explanation for certain vectorcardiographic events. This position of the "source" in relation to the "sink" depends upon the activation wave.[5]

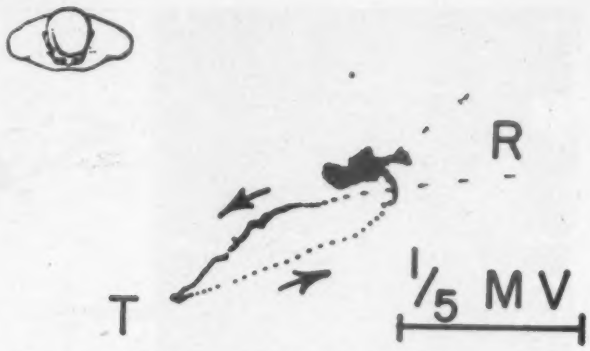


FIG. 9. Different speed of T loop limbs suggests a secondary change.

One of the characteristics of left bundle branch block is the absence of a Q wave in the left precordial leads.[6] We know from vectorcardiographic studies that this correlates with the leftward and anterior direction of the initial part of the QRS loop (Fig. 1). However, sometimes this initial part of the QRS loop behaves differently. Two additional situations may occur: either it is directed to the right, forming the Q loop; or it is completely absent and the initial portion of the loop is already the centrifugal limb of the R loop. In the first instance the rightward direction of the initial part of the QRS loop correlates very well with a shorter duration of the QRS loop (of our six cases, four had a duration of less than 120 milliseconds). Complete absence of any initial component, as in five of our cases, might also be found.

Correlation of QRS Vectors with Ventricular Activation in Left Bundle Branch Block: It is known that in left bundle branch block the right side of the heart is normally activated.[7] The activation of the right surface of the septum begins near the base of the anterior papillary muscle. It then spreads rapidly to the remainder of the right septal surface. Activation of the free ventricular wall follows septal activation. If the initial right to left septal activation is vector I and the right free ventricular wall activation is vector II, the resultant

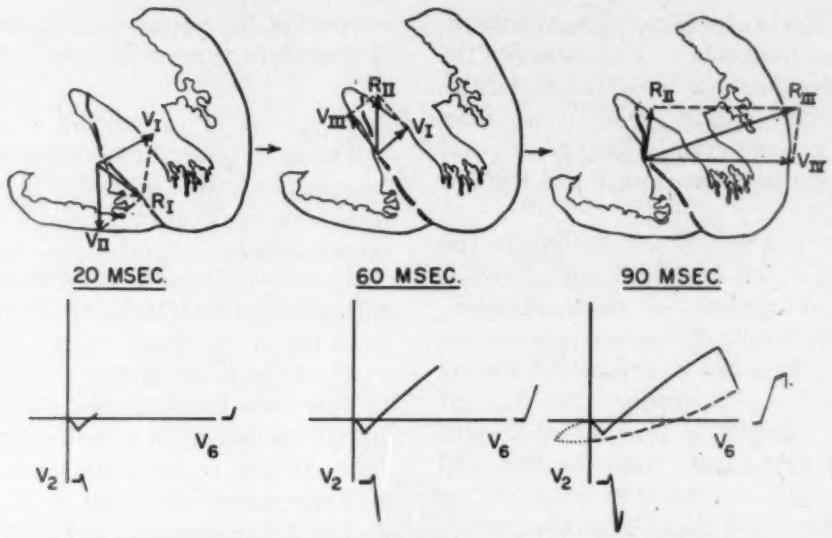


FIG. 10. An attempt to correlate different parts of the QRS loop with known steps of ventricular activation comparing the time of each one.

(RI) will be the long axis of the initial part of the QRS loop. It is directed anteriorly and either to the left (initial component) or to the right (Q loop), depending on the magnitude of the vectors (Fig. 10). In experimental studies the activation of left bundle branch block starts near the base of the anterior papillary muscle and twenty milliseconds later it reaches the trabecular zone of the right ventricle, which coincides with the duration of the initial deflection of the QRS loop in our cases.[7] Theoretically, it seems reasonable that the duration and the direction of the initial part of the QRS loop should depend upon the magnitude-time relationship of the vectors I and II. These factors will determine either the absence of the initial component or its presence, its size and spatial orientation. This explanation is purely theoretical; however, it is reasonable to say that this depends upon the over-all magnitude of the septal vector forces developed from right to the left.[8]

We know from experimental studies[7] that the electrical activation arrives at the base of the right ventricle fifty or sixty milliseconds after its onset (vector III) at which time vector I persists but vector II has disappeared. The resultant of III and I will be directed to the left, posteriorly and either superiorly or inferiorly, depending again upon the magnitude-time relationship of I and III. The resultant is the centrifugal limb of the R loop, the end of which may correspond with the termination of right ventricular activation (which is predominantly septal) (Fig. 10). At this time there is a tremendous potential gradient between the depolarized right ventricle and the resting left ventricle. According to the views of Rodrigues and Sodi-Pallares,[9] there is a physiologic "barrier" between each side of the septum, which becomes manifested when a block is produced.

Arriving at this boundary the wave finds its passage greatly impeded but apparently it is finally able to "jump this barrier." The time required for this process accounts for most of the delay noted in the bundle branch block. This blocking of the activation wave in bundle branch block takes place in a very limited area located in the septum at the border of the two muscular masses derived from the two ventricles.[9] In left bundle branch block, after having "jumped" the physiologic "barrier" the activation takes a long time to reach the left septal surface. The time spent for the formation of the plateau in our cases correlates very well with the "jump" of the physiologic "barrier" in experimental studies.[7] When the "jump" occurs, we have a deviation of the main vector superiorly and anteriorly and this displacement is caused by the left ventriclar activation. Vector IV, which is directed to the left, superiorly and either anteriorly or posteriorly, swings upward and to the front. This corresponds to the invasion of the free wall of the left ventrical and, in our cases, to the centripetal limb (Fig. 10). This limb is formed by vectors of progressively diminishing magnitude due to decrease of the potential gradient between the ventricles.[5] On the average, the duration of the

QRS loop until the beginning of the centripetal limb is 100 milliseconds. The average of sixty-three milliseconds that we obtained for the centripetal limb corresponds grossly to the time of left ventricular activation. The centripetal limb of the R loops continues until the J point, (Fig. 5).

The clockwise rotation of the R loop in the horizontal plane in left bundle branch block is probably a characteristic of this condition. It has been stated that this is not always the case;[10] however, from the experimental studies of activation it would appear that in left bundle branch block the base of the right ventricle is activated earlier than the free wall of the left ventricle contrary to what occurs normally. If there is a slight degree of delay, but the free left ventricular wall is activated earlier than the base of the right ventricle, this should not be called left bundle branch block.[6] We think, therefore, that any left bundle branch block, be it of the complete or incomplete type, must have a clockwise rotation in the horizontal plane.

The centrifugal limb of the R loop correlates with the spread of the activation through the right septum and other portions of the right ventricle. It is possible that at this time some part of the left ventricular septum has already been activated. After arriving at the left septal surface the activation spreads rapidly, extending over the left parietal endocardium. This causes the appearance of vector IV, swinging the R loop superiorly and anteriorly (Fig. 10). The duration of the plateau correlated well with the duration of the QRS loop.

Primary and Secondary ST-T Changes in Left Bundle Branch Block: It has been suggested that secondary ST-T changes in the vectorcardiogram would be manifested by rotation within the same plane, that is, without torsion.[11] This is frequently the case in ventricular premature contractions. It also has been suggested that the primary type of the T loop is twisted in relationship to the QRS loop. This has been found in cases of myocardial infarction.[11] With few exceptions, the T loop of our vectorcardiograms was always in the same spatial plane as the QRS loop. This absence of torsion had been noted previously in left bundle branch block. This is because the secondary ST-T changes are so intense that they almost completely obliterate the primary ST-T changes. We want to emphasize the difficulty in demonstrating the presence of a primary type of T loop in this group of patients.

Summary

Thirty vectorcardiograms of left bundle branch block were studied. The time, direction, sense and position of the Q, R and ST-T loops were studied.

Twenty-five cases had QRS loops with greater duration than 120 milliseconds and five ranged from 100 to 120 milliseconds.

The Q loop was present in six cases. Nineteen of the vectorcardiograms had a characteristic initial component directed anteriorly and to the left. In five vectorcardiograms the initial part was the centrifugal limb of the R loop.

The R loop rotated clockwise in the horizontal and sagittal planes and counterclockwise in the frontal plane. It was directed to the left, posteriorly and superiorly. Dividing it into initial component, centrifugal limb, plateau and centripetal limb, the two last portions were the most delayed. The initial component was very characteristic of this condition. The plateau correlated very well with the total delay. The longer the QRS loop, the longer the plateau and the more frequent its occurrence.

The J point and the T loop were always opposite to the R loop. In general, important torsion of the T loop was found, indicating secondary changes. In most of the cases the T loop had a slow centrifugal limb and a rapid centripetal limb.

A correlation with ventricular activation and an explanation of the vectorcardiographic behavior were given.

References

1. Grishman, A. and Scherlis, L. Spatial Vectorcardiography, p. 12. Philadelphia, 1952. W. B. Saunders Co.
2. Cabrera, E., Garcia-Font, R., Gaxiola, A. and Pileggi, F. The vectorcardiogram of ventricular activation in chronic coronary heart disease. *Am. Heart J.*, 55: 557, 1958.
3. Sodi-Pallares, D., Rodrigues, M. I., Chait, O. and Zuckerman, R. The activation of the interventricular septum. *Am. Heart J.*, 41: 659, 1951.
4. Mascarenhas, A. S. Quoted in Reference 7, p. 511.
5. Cabrera, E. and Gaxiola, A. Metodo para correlacionar el vectorcardiograma con el proceso de la activation ventricular. *Arch. Inst. cardiol. Mexico*, 28: 469, 1958.
6. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F.,

ERLANGER, H., HECHT, H., COTRIN, N., BARKER, P. S., SCARSI, R. and MENESES DE OLIVERIRA, R. The precordial electrocardiogram. *Am. Heart J.*, 27: 19, 1944.

7. SODI-PALLARES, D. and CALDER, R. M. New Bases of Electrocardiography, pp. 407, 413. St. Louis, 1956. C. V. Mosby Co.
8. DICKENS, J., MARANHAO, V. and GOLDBERG, H. Ventricular endocardial leads in left bundle branch block and left ventricular hypertrophy. *Am. J. Cardiol.*, 3: 472, 1959.
9. RODRIGUES, M. I. and SODI-PALLARES, D. The mechanism of complete and incomplete bundle branch block. *Am. Heart J.*, 44: 715, 1952.
10. SCHERLIS, L. and GRISHMAN, A. Spatial vectorcardiography. Left bundle branch block and left ventricular hypertrophy. *Am. Heart J.*, 41: 494, 1951.
11. NIMURA, T. A vectorcardiographic analysis of left ventricular strain pattern comparatively studied with ST-T change of left bundle branch block and ventricular premature beat of right ventricular origin. *Am. Heart J.*, 57: 552. 1959.

The Electrocardiogram, Vectorcardiogram and Ventricular Gradient in Combined Pulmonary Stenosis and Interatrial Communication*

GEORGE E. BURCH, M.D. *and* NICHOLAS P. DEPASQUALE, M.D.

New Orleans, Louisiana

WHEN PULMONARY STENOSIS is associated with an interatrial communication, the communication in the atrial septum is either due to valve patency of the foramen ovale or to an ostium secundum or primum defect. From the reports in the literature it would seem that valve patency of the foramen ovale is more often the cause of an interatrial right to left shunt in the presence of pulmonary stenosis than is a true atrial septal defect.

Due to the elevation of right ventricular pressure and right atrial pressure and work with moderate to severe pulmonary stenosis, a right to left interatrial shunt develops if the valvula foraminis ovalis has failed to fuse completely with the septum secundum or if a true atrial septal defect is present. Under such circumstances it is difficult to determine clinically whether the shunt is through a valve patent foramen ovale or a true atrial septal defect. For this reason it is not possible to know accurately the incidence of combined pulmonary stenosis and true atrial septal defect.

In the presence of an uncomplicated atrial septal defect with left to right shunt the crista supraventricularis frequently hypertrophies, resulting in functional infundibular stenosis. This cause for obstruction to right ventricular outflow is not considered in this study. It is necessary to distinguish, however, between congenital pulmonary stenosis with atrial septal defect and atrial septal defect with secondary infundibular pulmonary stenosis.

There are so few reports in the literature of the electrocardiogram in pulmonary stenosis with true atrial septal defect that we considered it of interest to review the electrocardiogram and spatial vectorcardiogram of patients with pulmonary stenosis and interatrial communication at the Charity Hospital of Louisiana. Previous reports from this laboratory described the electrocardiogram and spatial vectorcardiogram in uncomplicated atrial septal defect[1,2] and the electrocardiogram in isolated pulmonary stenosis.[3]

Most reports dealing with pulmonary stenosis and interatrial communication do not clearly distinguish between a patent foramen ovale and a true ostium primum or secundum defect because of the difficulties in diagnosis in the presence of a right to left shunt without previous information concerning a left to right interatrial shunt, autopsy data or surgical exploration. Selzer et al.[4] in a review of the literature described twenty-nine patients with pulmonary stenosis who had a patent foramen ovale demonstrated at autopsy. The authors mentioned no patients with true congenital interatrial septal defect. Engle and Taussig[5] reported three cases of patients with pulmonary stenosis and interatrial communication due to patent foramen ovale established at autopsy. Callahan and co-workers[6] studied ten patients with pulmonary stenosis and interatrial communication with right to left shunt and commented on the difficulty of distinguishing between pulmonary stenosis with a patent foramen ovale and pulmonary stenosis with atrial septal defect in

* From the Department of Medicine, Tulane University School of Medicine and the Charity Hospital of Louisiana in New Orleans. Supported by grants from the United States Public Health Service.

patients in whom the shunt is entirely right to left. Johnson and Johnson[7] described five patients with pulmonary stenosis and cyanosis, all of whom were found to have a patent foramen ovale at autopsy.

Broadbent et al.[8] indicated that whereas pulmonary stenosis is commonly associated with a defect of the atrial or ventricular septum, few cases have been reported in which the intracardiac shunt was left to right. They presented hemodynamic data of five patients with pulmonary stenosis and left to right interatrial shunt. The mean right ventricular systolic pressure in these patients was 74 mm. Hg (range, 48 to 158 mm. Hg). In spite of a significant degree of pulmonary stenosis the pulmonary artery pressure and flow were either within normal limits or increased. The electrocardiograms of three of these patients were typical of right ventricular hypertrophy; right bundle branch block was present in one patient and the electrocardiogram was not remarkable in the fifth.

Moffitt et al.[9] described two patients with valvular pulmonary stenosis and atrial septal defect. They stated that the electrocardiograms from these patients showed right ventricular hypertrophy. Rudolph and associates[10] studied seven patients with valvular pulmonary stenosis and atrial septal defect in whom the right ventricular pressures ranged between 36 and 62 mm. Hg. The electrocardiograms of all the patients were interpreted to display incomplete right bundle branch block. The R′ wave in lead V_1 was usually of great magnitude. Magidson and co-workers[11] noted complete or incomplete right bundle branch block in four of the eight patients with pulmonary stenosis and atrial septal defect that they studied. None of the three patients described by Eldridge and Hultgren[12] had an RSR′ or "incomplete right bundle branch block" pattern in lead V_1. In fact, the electrocardiograms from these patients closely resembled those of uncomplicated pulmonary stenosis. However, the mean right ventricular systolic pressure in this latter series was 81 mm. Hg, whereas in the series mentioned previously in which all of the patients had "incomplete right bundle branch block" the mean right ventricular pressure was 53 mm. Hg. Deuchar and Zak[13] concluded that in the presence of pulmonary stenosis with increased pulmonary blood flow a true atrial septal defect as the cause of the increased blood flow is very rare. Joly et al.[14] found all of thirteen patients with pulmonary stenosis and interatrial communication (trilogy of Fallot in the French literature) to have right to left interatrial shunts. Two patients had an associated left to right shunt. They failed to describe the anatomic defect. Abrahams and Wood[15] described five patients with valvular pulmonary stenosis and left to right interatrial shunt. In most of these patients the electrocardiogram resembled that of uncomplicated atrial septal defect. However, in one patient a tall R wave in lead V_1 suggested pulmonary hypertension or stenosis.

TABLE I

Age, Sex and Race Distribution of Thirty-One Patients with Pulmonary Stenosis and Interatrial Communication

Age Group (Years)	No. of Patients	Sex		Race	
		Men	Women	White	Negro
0–1	3	1	2	1	2
1–5	5	3	2	2	3
6–10	4	2	2	2	2
11–20	10	8	2	7	3
21–30	5	3	2	2	3
31–40	3	2	1	2	1
41–50	1	1	...	...	1
Total	31	20	11	16	15

In thirty patients with atrial septal defect Kjellberg and associates[16] found three patients with an associated mild pulmonary stenosis. The authors did not mention the type of pulmonary stenosis; therefore, it is not known if these patients represented instances of atrial septal defect with functional infundibular stenosis due to hypertrophy of the crista supraventricularis or whether there was true pulmonary valvular stenosis. In a fourth patient with a large atrial septal defect not included in the original series, a mild infundibular stenosis, probably functional, was demonstrated at autopsy.

Brock[17] classified pulmonary valvular stenosis with normal aortic root as being associated with either closed atrial septum or interatrial communication, thus avoiding exact anatomic definition of the atrial septal defect. He did mention, however, that in most instances the defect was due to an incompetent foramen ovale and only rarely was a true atrial septal defect present.

It is evident that whereas pulmonary stenosis with patency of the foramen ovale as a cause of a

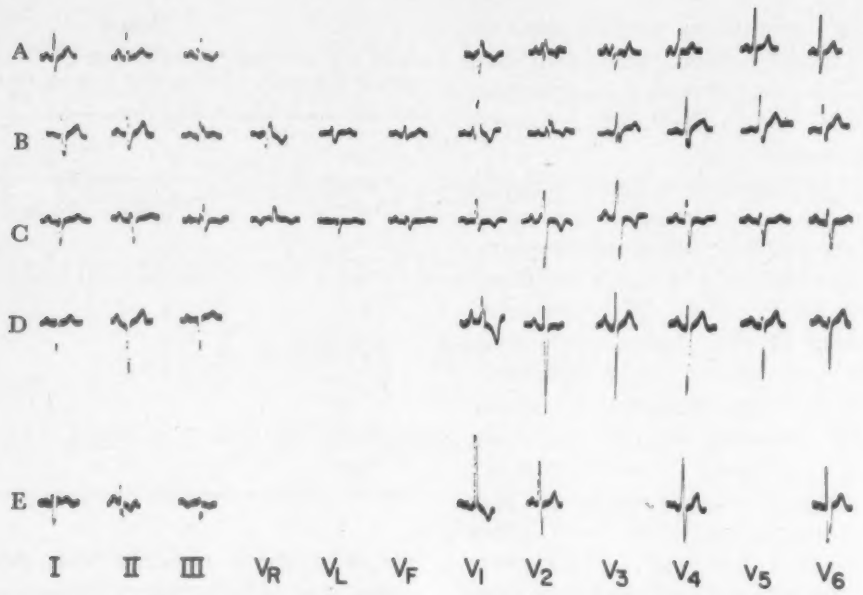


FIG. 1. Various electrocardiographic patterns in patients with pulmonary stenosis and interatrial communication. A, Case 4; B, Case 18; C, Case 12; D, Case 13; E, Case 15. See text for details.

right to left shunt is not an uncommon finding, relatively few patients with pulmonary stenosis and either right to left or left to right interatrial shunts through a true atrial septal defect have been reported. Most, if not all, of the patients with pulmonary stenosis and right to left interatrial shunt that have undergone autopsy had a patent foramen ovale. Nevertheless, patients with interatrial right to left shunt through a true atrial septal defect are probably not as rare as the literature would suggest. The distinction is important because reduction of the right ventricular pressure secondary to pulmonary valvulotomy should result in functional closure of the foramen ovale and disappearance of the shunt. However, in the presence of a true atrial septal defect the intracardiac shunt will persist as a left to right shunt. In fact, two patients to be reported in this paper had pulmonary stenosis with right to left interatrial shunt prior to pulmonary valvulotomy and a left to right shunt after surgery. It is important to know, in patients with pulmonary stenosis, if a left to right interatrial shunt is present because reduction of the pulmonary stenosis without closure of the atrial septal defect would result in an increase in the magnitude of the left to right shunt.

MATERIAL AND METHODS

Thirty-one patients with pulmonary stenosis and interatrial communication constituted the material for this study. Cardiac catheterization showed

TABLE II

Electrocardiographic Findings in Thirty-One Patients with Pulmonary Stenosis and Interatrial Communication

Interatrial Shunt	No. of Patients	Q Wave in Lead V_1 or V_2	P Wave >2.3 mm. in Lead II or III	P-R Interval Prolonged	Intrinsicoid Deflection in Lead V_1 Delayed*	Mean QRS Duration (sec.)
Right to left	20	10 (50%)	11 (55%)	1 (5%)	16 (80%)	0.089
Left to right	11	1 (9%)	1 (9%)	1 (9%)	8 (72%)	0.101

* An intrinsicoid deflection in lead V_1 of over 0.032 second in children (to fifteen years of age) and over 0.04 second in adults was considered delayed.

† The R/S ratio in lead V_1 was considered to be abnormally large when it was 4 or greater in children up to five years of age. Beyond five years of age a ratio of unity or greater was abnormal.[26]

eleven patients to have left to right interatrial shunt and twenty, right to left shunt. Two of the latter patients had an associated small left to right interatrial shunt. Four of the patients had angiocardiographic studies. Twenty of the patients underwent cardiac surgery and three patients were submitted to autopsy.

The mean age of the patients was sixteen years (range, two months to forty-five years) (Table I). Twenty patients were men and eleven were women. Sixteen were white and fifteen, Negro.

All of the patients had routine electrocardiograms recorded within a few days of cardiac catheterization. The ventricular gradient ($\hat{G}$) was obtained for all the tracings by methods previously described.[18,19] The normal values for the direction and magnitude of $\hat{A}QRS$ and $\hat{G}$, as indicated in previous reports,[19,20] are as follows: mean direction of $\hat{A}QRS$, +41.7° (range, −21.5° to +104.9°); mean magnitude of $\hat{A}QRS$, 21.8 μv.s. (40.6 to 3.1 μv.s.); mean direction of $\hat{G}$, +39.2° (+72.2° to +2.2°); mean magnitude of $\hat{G}$, 42.2 μv.s. (78.9 to 13.5 μv.s.). Spatial vectorcardiograms were recorded from ten patients employing the equilateral tetrahedral reference system.[21]

Results

The Electrocardiogram

The results are summarized in Figure 1 and Table II.

1. Pulmonary Stenosis with Right to Left Interatrial Shunt: This type of lesion was present in twenty patients.

P wave: The P-R interval was prolonged in one patient and there were no disturbances in rhythm. The P wave exceeded 2.3 mm. in amplitude in lead II or III in eleven patients (55 per cent).

QRS complex: The QRS complex was not prolonged in any of the patients. However, one patient with a QRS duration of 0.10 second had an rsR′ complex in V_1.

Lead I displayed a small R wave and a narrow S wave of large magnitude. In only one patient was the magnitude of the R wave in this lead greater than that of the S wave. In lead III a small Q wave preceded an R wave of large magnitude in the majority of patients. An S wave was present in lead III in eight patients (40 per cent).

A Q wave in V_1, considered as evidence of right atrial hypertrophy by some investigators, was present in ten patients (50 per cent). An R wave of great magnitude without an associated S wave in lead V_1 was noted in eighteen of the twenty patients (qR in ten patients, R in eight patients). In two patients there was a small R wave and an S wave of large magnitude in V_1. The R/S ratio in lead V_1 (corrected for age) was greater than normal in eighteen patients (90 per cent) and the intrinsicoid deflection was late in sixteen patients (80 per cent). In leads V_5 and V_6 the R waves were small and the S waves were of large magnitude (Fig. 1C,D). In only seven patients (35 per cent) was the R wave in lead V_6 greater than the S wave. The mean R/S ratio for lead V_6 was 2.5.

T wave: There was little abnormality of the T waves. The T wave was usually positive in lead I and negative in lead III. The T wave in lead V_1 was deeply inverted. This in association with the tall R wave in V_1 constituted the so-called right ventricular systolic overload pattern (Fig. 1D,E). All except two patients had such a configuration. The T waves in the remainder of the precordial leads with the exception of lead V_2 were usually upright.

Comment: The electrocardiogram of patients with pulmonary stenosis and right to left interatrial shunt tended to be very similar to that of patients with isolated pulmonary stenosis

Table II (*Continued*)

Mean R/S Ratio in Lead V_1	Abnormal R/S Ratio V_1†	"Right Bundle Branch Block Delay"	Mean R/S Ratio in Lead V_6	RV Systolic Pressure (mm. Hg)	Mean Left to Right Shunt PBF/SBF‡	Mean Right to Left Shunt (% SVR)§
14.9	18 (90%)	1 (5%)	2.5	133	...	41
7.1	9 (82%)	9 (82%)	5.2	68	1.6	...

‡ PBF = pulmonary blood flow; SBF = systemic blood flow.
§ SVR = Systemic venous return.

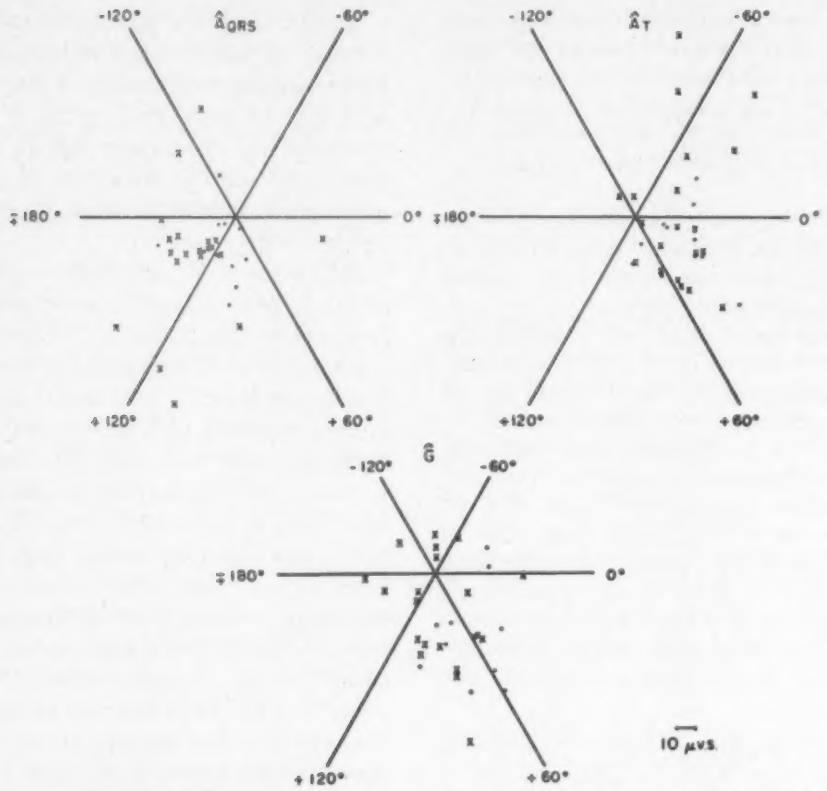


FIG. 2. ÂQRS, ÂT and Ĝ in the frontal plane in thirty-one patients with pulmonary stenosis and interatrial septal defect. • = patients with left to right shunt; × = patients with right to left shunt.

and right ventricular systolic pressure greater than 100 mm. Hg.[2] This relationship is not surprising since the defects are identical, the latter occurring in patients in whom the valvula foraminis ovalis has completely fused with the septum secundum, thus preventing a right to left interatrial shunt regardless of the level of the right atrial pressure. However, P waves of great magnitude in lead II or III and a Q wave of large magnitude in lead V_1 were much more frequent in the patients with pulmonary stenosis and right to left interatrial shunt than in patients with isolated pulmonary stenosis. If these findings are reliable electrocardiographic signs of right atrial hypertrophy, then right atrial hypertrophy is greater in the presence of a right to left interatrial shunt.

It is important to distinguish patients with pulmonary stenosis and right to left interatrial shunt from those with the pulmonary stenosis in tetralogy of Fallot. Again the electrocardiograms of patients with these two types of defects may be very similar. The fact that the ventricular septum is intact in pulmonary stenosis with interatrial shunt has led some investigators to suppose that the degree of right ventricular hypertrophy is greater in patients with pulmonary stenosis and interatrial shunt than in patients with tetralogy of Fallot. In tetralogy of Fallot a ventricular septal defect imposes a "ceiling" on the right ventricular pressure. The degree of right ventricular hypertrophy has not been helpful in differentiating these two defects electrocardiographically. In both defects the right ventricular hypertrophy is marked and the variations great.

A study of the electrocardiograms of 140 patients with tetralogy of Fallot[22] showed that certain electrocardiographic manifestations may assist in the differential diagnosis of pulmonary stenosis with interatrial septal defect and tetralogy of Fallot. For example, in tetralogy of Fallot electrocardiographic signs of extreme clockwise rotation of the heart are common. These include a Q wave of large magnitude in lead III and the absence of a septal Q wave in leads I, VL and V_6. In pulmonary stenosis with right to left interatrial shunt a Q wave in lead III when present was not of unusual magnitude. Furthermore, an S wave in lead III was extremely rare (7 per cent) in tetralogy of Fallot but was present in 40 per cent of the

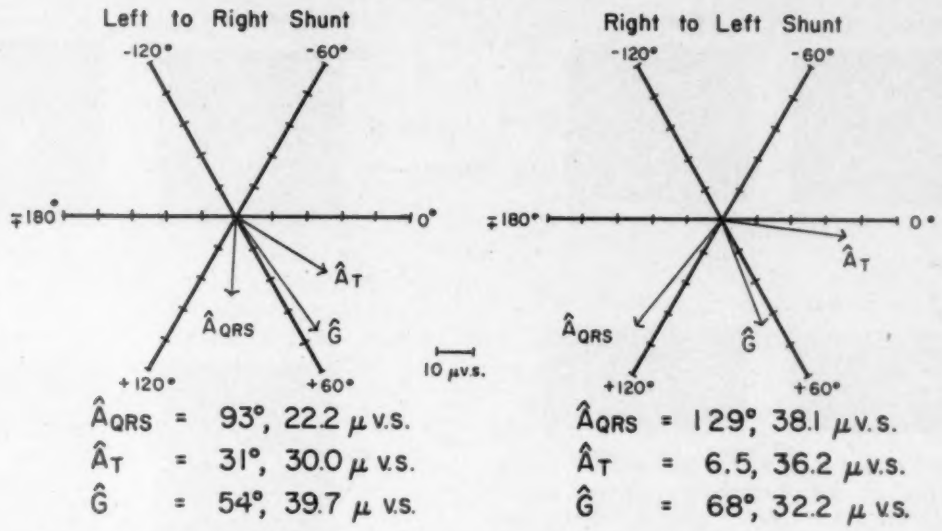


FIG. 3. Mean $\hat{A}QRS$, $\hat{A}T$ and $\hat{G}$ in the frontal plane in patients with pulmonary stenosis and interatrial septal defect.

patients with pulmonary stenosis and an atrial shunt. Initial notching of the R wave in lead V_1 was more frequently observed in tetralogy of Fallot than in pulmonary stenosis with an interatrial shunt.

Several authors[23] have emphasized the fact that in pulmonary stenosis with interatrial septal defect the T wave may be negative in lead V_1 but is usually positive in the remainder of the precordial leads, whereas in pulmonary stenosis and interatrial shunt the T waves are negative in several precordial leads recorded from points to the left of V_1. In the present study the T waves in the precordial leads were not consistently different from those of 140 patients with tetralogy of Fallot previously studied.[21]

Medrano[24] has called attention to elevation of the RS-T segment in leads I and aVL in some patients with pulmonary stenosis and interatrial right to left shunt. Although the significance of this finding is not known, it was present in four of these twenty patients with pulmonary stenosis and interatrial shunt. This was not observed in the 140 patients with tetralogy of Fallot. This sign (Fig. 1E) may be of some value in differentiating the two defects electrocardiographically.

Because of the right to left interatrial shunt more blood reaches the left ventricle than the right. According to the hemodynamic concept of Cabrera and Monroy[25] this should result in diastolic overloading of the left ventricle. They indicated that the electrocardiographic expressions of diastolic overloading of the left ventricle consist of R waves of large magnitude with positive high and peaked T waves in leads V_5 and V_6. None of the twenty patients studied had such a configuration in leads V_5 and V_6.

Since the left ventricle is normally developed in pulmonary stenosis with interatrial communication, whereas it is hypoplastic in tetralogy of Fallot, electric manifestations of left ventricular activity would be expected to be more evident in the former defect than in the latter. Although most of the patients had rS complexes in leads V_5 and V_6, in five patients the magnitude of the R wave exceeded that of the S wave, an exceptional finding in tetralogy of Fallot.

Although certain electrocardiographic manifestations of congenital heart disease can be explained by alterations in the spatial orientation of the muscle masses of the heart due to rotation, dynamic factors such as the work, tension and power developed by the myocardium must also play a role in determining the configuration of the electrocardiogram.

2. Pulmonary Stenosis with Left to Right Interatrial Shunt: This type of lesion was present in eleven patients.

P wave: The P-R interval was prolonged in one patient. There were no disturbances in rhythm. The P wave in lead II or III exceeded 2.3 mm. in only one patient and a Q wave was present in lead V_1 in the same patient.

QRS complex: The mean QRS duration was 0.10 second. There was a small R wave and a prominent S wave in lead I. The S wave in this lead was usually wide. In lead III there was an R wave associated with a small Q wave but usually there was no S wave (Fig.

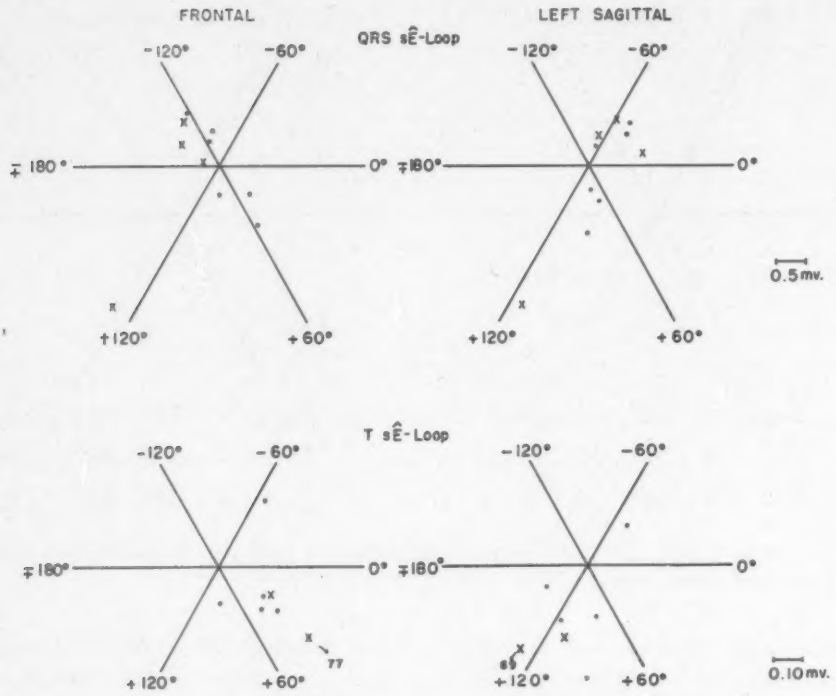


FIG. 4. Mean maximal instantaneous vectors of QRS and TsÊ loops for ten patients with pulmonary stenosis and interatrial communication. • = patients with left to right shunt; × = patients with right to left shunt.

1B). An rsR′ pattern was usually present in lead V_1 (Fig. 1A,B). The rsR′ configuration was present in lead V_1 in nine patients (82 per cent). The mean R/S ratio in lead V_1 was 7.1, being abnormal in nine patients (82 per cent). There were well developed R waves associated with moderately deep and wide S waves in leads V_5 and V_6.

T wave: With the exception of inversion of the T wave in lead V_1 in nine patients, there were no abnormalities of the T wave.

Comment: The electrocardiogram in pulmonary stenosis and atrial septal defect appears to be very similar to that of uncomplicated atrial septal defect. However, in some patients manifestations of both defects are evident in the electrocardiogram. In one patient with a right ventricular systolic pressure of 105 mm. Hg, valvular pulmonary stenosis and a left to right interatrial shunt amounting to 1.3 times systemic blood flow and no right to left shunt, a qR complex of the type seen in pulmonary stenosis was recorded in lead V_1. In addition a wide S wave, frequent in atrial septal defect but not in pulmonary stenosis, was present in lead I. In another patient with a right ventricular systolic pressure of 70 mm. Hg, valvular pulmonary stenosis and a left to right interatrial shunt equal to 0.7 times the systemic blood flow, the R′ wave in V_1 was of the magnitude seen in isolated pulmonary stenosis (Fig. 1B). The electrocardiogram of this patient resembled that of patients with isolated pulmonary stenosis except for the wide QRS complexes (QRS duration = 0.11 second). Thus, in this patient the presence of the combined defects modified the electrocardiogram in a manner such that aspects of both atrial septal defect (rsR′ and wide QRS complexes) and pulmonic stenosis (R′ in V_1 of large magnitude and deeply inverted T wave in lead V_1) were evident in the electrocardiogram. However, patients with atrial septal defect and functional infundibular pulmonary stenosis may have similar electrocardiograms.[1]

In the remaining patients the right ventricular systolic pressures ranged between 48 and 90 mm. Hg and with the exception of one patient who had a normal electrocardiogram their electrocardiograms resembled those previously described for uncomplicated ostium secundum defect.[1]

THE VENTRICULAR GRADIENT

The results of the studies of the ventricular gradient are summarized in Figures 2 and 3.

1. Pulmonary Stenosis with Right to Left Interatrial Shunt (twenty patients): In sixteen

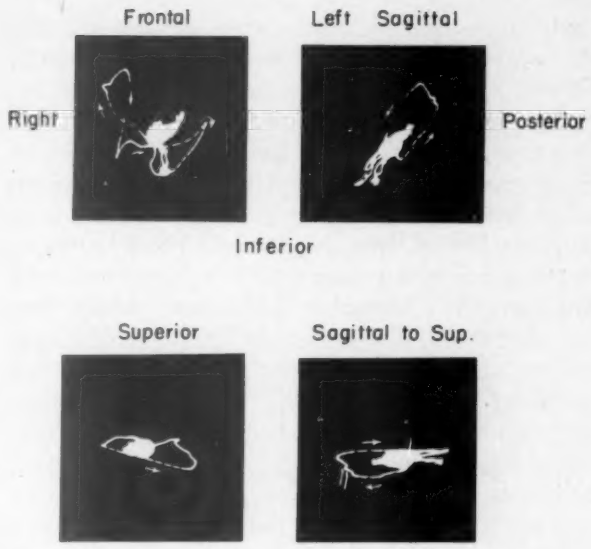


FIG. 5. Spatial vectorcardiogram of a patient with pulmonary stenosis and an ostium secundum type of atrial septal defect (Case 5, Table III). Note the orientation of the QRSsÊ loop superiorly and to the right in the frontal plane projection. This and Figures 6, 7 and 8 show the left sagittal projection of the superior plane of the tetrahedron.

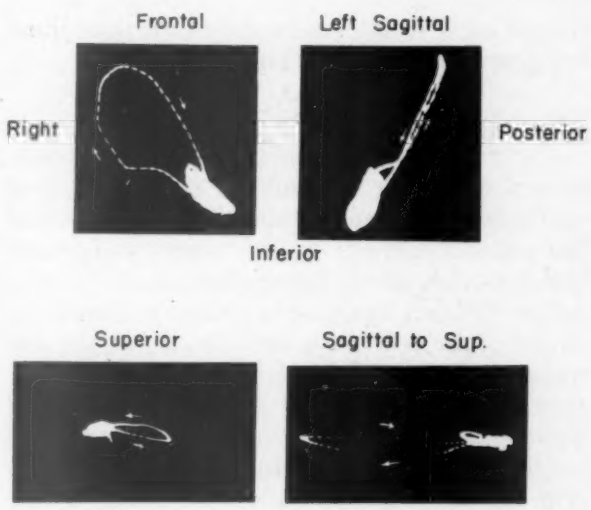


FIG. 6. Spatial vectorcardiogram of a patient with pulmonary stenosis and patent foramen ovale (Case 13, Table III). The QRSsÊ loop is characteristically oriented superiorly, posteriorly and to the right.

patients the ÂQRS was directed inferiorly and to the right in the frontal plane. It was directed superiorly and to the right in two patients, and ÂQRS was directed inferiorly and to the left in two other patients (Fig. 2). ÂQRS was directed more to the right than normal in all except two patients. In eighteen of the twenty patients ÂQRS was located to the right of Ĝ. The angle between ÂQRS and Ĝ exceeded

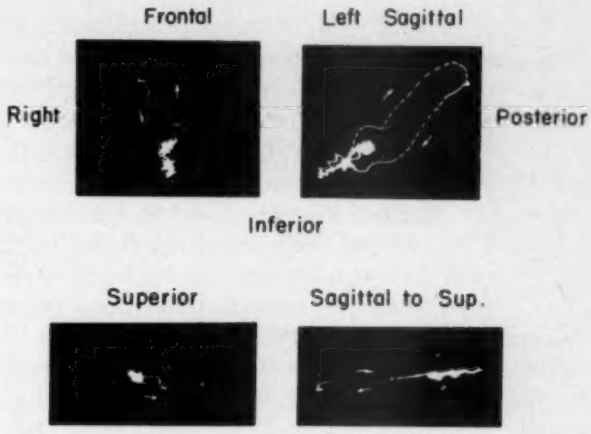


FIG. 7. Spatial vectorcardiogram of a patient with pulmonary stenosis and an ostium secundum type of atrial septal defect (Case 9, Table III). The QRSsÊ loop is characteristically oriented superiorly and to the right in the frontal plane projection.

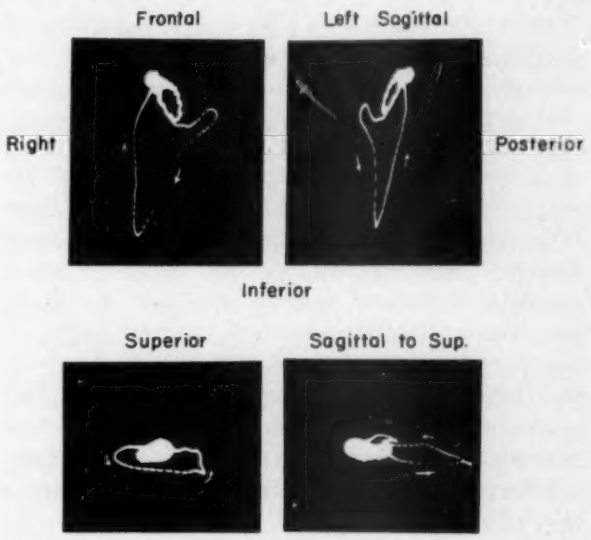


FIG. 8. Spatial vectorcardiogram of a patient with an uncomplicated atrial septal defect. In this type of defect the QRSsÊ loop is oriented inferiorly and slightly to the right in the frontal plane projection.

35° in eleven patients (55 per cent). ÂT was directed superiorly almost 180° away from ÂQRS in eight patients. In the remaining patients it was directed inferiorly and to the left (Fig. 2).

The frontal plane projection of the ventricular gradient (Ĝ) was directed inferiorly and to the left in eight patients, inferiorly and to the right in seven patients, superiorly and to the right in three patients and superiorly and to the left in two patients (Fig. 2). The electrical position of Ĝ was abnormal in sixteen of the twenty patients (80 per cent), whereas Ĝ was abnormal in magnitude in two patients (10 per cent).

TABLE III

Maximal QRS and T Mean Instantaneous Vectors in Ten Patients with Pulmonary Stenosis and Interatrial Communication

Case No.*	QRSsÊ Loop				TsÊ Loop			
	Maximal Vector in Frontal Plane		Maximal Vector in Left Sagittal Plane		Maximal Vector in Frontal Plane		Maximal Vector in Left Sagittal Plane	
	Direction (degrees)	Magnitude (mv.)	Direction (degrees)	Magnitude (mv.)	Direction (degrees)	Magnitude (mv.)	Direction (degrees)	Magnitude (mv.)
5	−112	0.42	−70	0.34	−54	0.28	−45	0.19
7	43	0.70	72	0.62	36	0.25	90	0.38
8	90	0.48	87	0.42	...	...	...	...
9	−101	0.60	−38	0.86	89	0.12	151	0.16
21	−121	1.05	−44	1.00	33	0.18	115	0.21
23	57	1.20	90	1.14	45	0.20	80	0.18
16	−153	0.77	−73	0.52	...	...	...	...
13	−128	0.93	−59	0.94	27	0.20	108	0.26
17	−162	0.31	−12	0.97	...	...	...	...
22	128	3.00	116	2.60	38	0.77	129	0.69
Average	−46	0.95	7	0.94	31	0.29	90	0.30

* The first six patients had left to right interatrial shunts, whereas the last four patients had right to left shunts.

2. Pulmonary Stenosis with Left to Right Interatrial Shunt (eleven patients): ÂQRS was directed inferiorly and to the right in seven patients, inferiorly and to the left in three patients and superiorly and to the right in one patient (Fig. 2). ÂQRS was located to the right of Ĝ in all except one patient. The angle between ÂQRS and Ĝ exceeded 35° in five patients (45 per cent). ÂT was located inferiorly and to the left in most of the patients (Fig. 2).

The ventricular gradient was directed inferiorly and to the left in the frontal plane projection in eight patients, superiorly and to the left in two patients and inferiorly and to the right in one patient. Ĝ was abnormal in direction in five patients (45 per cent) and was normal in magnitude in all patients.

Comment: Ĝ was abnormal in 80 per cent of the twenty patients of this study in whom the severity of the pulmonary stenosis was such that there was right to left interatrial shunt. Of the eleven patients with left to right interatrial shunts only 45 per cent had an abnormal Ĝ. Two of these patients had a moderately elevated right ventricular systolic pressure (105 and 90 mm. Hg).

The ÂQRS was deviated more to the right and the ÂT more to the left in the frontal plane projection in the patients with pulmonary stenosis and right to left interatrial shunt than those with left to right shunt (Fig. 3).

THE SPATIAL VECTORCARDIOGRAM

The results of the studies of the spatial vectorcardiogram in ten patients are summarized in Figures 4 through 8 and Table III. Six of the patients had left to right interatrial shunts and four had right to left shunts.

The QRSsÊ loops were oriented superiorly, to the right and posteriorly in six of the ten patients (Fig. 4). Of the remaining patients, three had QRSsÊ loops which were oriented inferiorly, to the left and vertically and one had a QRSsÊ loop oriented inferiorly, to the right and anteriorly. The mean direction of the maximal mean instantaneous vector of the QRSsÊ loop in the frontal plane projection was −46° and the mean magnitude 0.95 mv., whereas the mean direction of this vector in the left sagittal plane was +7° and the mean magnitude 0.94 mv. (Table III). There was considerable distortion of the QRSsÊ loop in three patients (Fig. 5). The loop was inscribed in a counterclockwise direction in the frontal plane projection in four patients and in a clockwise direction in six patients.

The TsÊ loop was inscribed in sufficient detail for analysis in seven patients. It was oriented inferiorly, to the left and anteriorly in six

patients and superiorly and to the left in one patient (Fig. 4).

Comment: The most characteristic feature of the spatial vectorcardiogram in pulmonary stenosis with interatrial communication was the orientation of the QRSsÊ loop superiorly and to the right in the frontal plane projection in six of the ten patients. In thirty-three patients with tetralogy of Fallot such an orientation of the QRSsÊ loop never occurred. The spatial vectorcardiogram, therefore, is of value in differentiating these two defects which are so similar clinically. The only other patients that we have studied in whom the QRSsÊ loops were oriented superiorly and to the right in the frontal plane projection were patients with severe pulmonary hypertension. Figure 6 shows the spatial vectorcardiogram of a thirteen year old white boy with pulmonary stenosis and right to left interatrial shunt and a right ventricular systolic pressure of 160 mm. Hg. The QRSsÊ loop is oriented superiorly, to the right and posteriorly. The TsÊ loop is oriented 180° away from the QRSsÊ loop. Figure 7 is the spatial vectorcardiogram from a patient with an ostium secundum defect and a mild pulmonary valvular stenosis confirmed by surgery. This patient had a right ventricular systolic pressure of 55 mm. Hg; obviously, more than the magnitude of the right ventricular pressure is responsible for the similarity in spatial orientation of the spatial vectorcardiogram in these two types of defects. Figure 8 shows the spatial vectorcardiogram of a patient with uncomplicated ostium secundum defect which is included for comparison.

The reason for the specific spatial orientation of the QRSsÊ loop is not clear. This may be due in part to rotation of the apex of the heart posteriorly on its transverse axis and clockwise on its longitudinal axis. It is conceivable that in tetralogy of Fallot because of "underloading" of the left ventricle and lifting of the apex of the heart the main QRS vectors are oriented anteriorly, whereas in pulmonary stenosis with interatrial communication the "overloaded" left ventricle tends to result in enlargement of the left ventricle which displaces the heart posteriorly on its transverse axis so that the main QRS vectors are oriented posteriorly. However, the QRSsÊ loop was oriented superiorly and to the right in patients with left to right interatrial shunt; therefore, this explanation does not seem satisfactory and any attempts to explain the findings can only be conjectural.

General Comments and Hemodynamic Considerations

No significant correlation was found between magnitude of the right to left interatrial shunt and the right ventricular pressure ($r = 0.12$). Neither was there a significant correlation between the height of the P wave and either the right ventricular pressure ($r = 0.18$) or the magnitude of the right to left shunt ($r = 0.05$).

All of the patients with pulmonary stenosis and left to right interatrial shunt had a valvular pulmonary stenosis so that it was considered that there was an organic stenosis rather than a functional one secondary to hypertrophy of the crista supraventricularis. In addition, the atrial septum was explored at surgery and an ostium secundum defect found in two patients. A third patient was found to have a typical dome-shaped pulmonary stenosis at autopsy associated with a large ostium secundum defect. In these patients the electrocardiograms resembled those of pulmonary stenosis. However, the QRS complexes were wide in one patient so that the features of both pulmonary stenosis and atrial septal defect were evident in the electrocardiogram.

One patient with severe pulmonary stenosis and a right to left shunt, but no left to right shunt, was found to have an ostium secundum defect at surgery. Another patient with a right to left interatrial shunt developed a left to right shunt after pulmonary valvulotomy. This shunt was present four years after surgery. This patient either has a true atrial septal defect or the foramen ovale has remained separated even though the right ventricular pressure was only slightly elevated (40 mm. Hg) after surgery. A diminution in magnitude of the R wave in lead V_1 was the only electrocardiographic change that developed in the four years following surgery. Finally, right to left interatrial shunts persisted in two patients despite the reduction of the right ventricular pressure to normal following pulmonary valvulotomy.

From these data it can be seen that in the presence of pulmonary stenosis a right to left interatrial shunt may exist either through an ostium secundum defect or a valve-competent foramen ovale. It is not possible to determine clinically which of the two defects is responsible for the shunt so that the atrial septum should always be explored during surgery. A left to right interatrial shunt is always through a true atrial septal defect in patients with mild

valvular pulmonary stenosis. Eleven such patients were described in this study.

As far as is known only one patient with pulmonary stenosis and ostium primum defect has ever been described, but the electrocardiographic manifestations were not presented.[10] Such a combination of congenital defects should be associated with interesting electrocardiographic manifestations.

Summary

Valvular pulmonary stenosis may exist with either a right to left or a left to right interatrial shunt. The right to left shunt may be through a patent foramen ovale or a true atrial septal defect. The left to right shunt is through a true atrial septal defect.

The electrocardiograms of the patients with left to right shunt usually resembled those of patients with uncomplicated atrial septal defect. The electrocardiograms in patients with right to left shunt were quite similar to those seen in patients with pulmonary stenosis. However, in some of the latter patients the electrocardiogram manifested features of both pulmonary stenosis and an interatrial septal defect.

In many patients the QRSsÊ loop of the spatial vectorcardiogram was oriented superiorly, to the right and posteriorly. Such an orientation of the QRSsÊ loop was never seen in tetralogy of Fallot.

References

1. Burch, G. E. and DePasquale, N. The electrocardiogram and ventricular gradient in atrial septal defect. *Am. Heart J.*, 58: 190, 1959.
2. Burch, G. E. and DePasquale, N. P. The spatial vectorcardiogram in proved atrial septal defect. *Am. Heart J.*, 58: 319, 1959.
3. DePasquale, N. P. and Burch, G. E. The electrocardiogram and ventricular gradient in isolated pulmonary stenosis. *Circulation*, 21: 181, 1960.
4. Selzer, A., Carnes, W. H., Noble, C. A., Higgins, W. H. and Holmes, R. O. Syndrome of pulmonary stenosis with patent foramen ovale. *Am. J. Med.*, 6: 3, 1949.
5. Engle, M. A. and Taussig, H. B. Valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale; report of illustrative cases and analysis of clinical syndrome. *Circulation*, 2: 481, 1950.
6. Callahan, J. A., Brandenburg, R. O. and Swan, H. J. C. Pulmonary stenosis and interatrial communication with cyanosis; hemodynamic and clinical study of 10 patients. *Am. J. Med.*, 19: 189, 1955.
7. Johnson, R. P. and Johnson, E. E. Congenital pulmonic stenosis with open foramen ovale in infancy; report of 5 proved cases. *Am. Heart J.*, 44: 344, 1952.
8. Broadbent, J. C., Wood, E. H. and Burchell, H. B. Symposium on cardiac catheterization; left-to-right intracardiac shunts in presence of pulmonary stenosis. *Proc. Staff Meet. Mayo Clin.*, 28: 101, 1953.
9. Moffitt, G. R., Jr., Zinsser, H. F., Kuo, P. T. Johnson J. and Schnabel, T. G. Pulmonary stenosis with left to right intracardiac shunts. *Am. J. Med.* 16: 521, 1954.
10. Rudolph, A. M., Nadas, A. S. and Goodale, W. T. Intracardiac left-to-right shunt wih pulmonic stenosis. *Am. Heart J.*, 48: 808, 1954.
11. Magidson, O., Cosby, R. S., Dimitroff, S. P., Levinson, D. C. and Griffith, G. C. Pulmonary stenosis with left to right shunt. *Am. J. Med.*, 17: 311, 1954.
12. Eldridge, F. L. and Hultgren, H. N. Pulmonary stenosis with increased pulmonary blood flow. *Am. Heart J.*, 49: 838, 1955.
13. Deuchar, D. C. and Zak G. A. Cardiac catheterization in congenital heart disease; 4 cases of pulmonary stenosis with increased pulmonary blood flow. *Guy's Hosp. Rep.*, 101: 1, 1952.
14. Joly, F., Carlotti, J., Sicot, J. R. and Piton, A. Cardiopathies congenitales; les trilogies de Fallot. *Arch. mal. coeur*, 43: 687, 1950.
15. Abrahams, D. G. and Wood, P. Pulmonary stenosis with normal aortic root. *Brit. Heart J.*, 13: 519, 1951.
16. Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B. Diagnosis of Congenital Heart Disease, p. 344. Chicago, 1955. Year Book Publishers.
17. Brock, R. C. The Anatomy of Congenital Pulmonary Stenosis, p. 26. New York, 1957. Hoeber.
18. Wilson, F. N., Macleod, A. G., Barker, P. S. and Johnston, F. D. The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. *Am. Heart J.*, 10: 46, 1934.
19. Ashman, R. A statistical study of the ventricular gradient and the QRS complex of the electrocardiogram. *Arch. Inst. cardiol. Mexico*, 15: 266, 1945.
20. DePasquale, N. P. and Burch, G. E. A study of the ventricular gradient in normal infants and children. *Am. J. Cardiol.*, 5: 464, 1960.
21. Burch, G. E., Abildskov, J. A. and Cronvich, J. A. Spatial Vectorcardiography, p. 84. Philadelphia, 1953. Lea & Febiger.
22. DePasquale, N. and Burch, G. E. The electrocardiogram, spatial vectorcardiogram and ventricular gradient in tetralogy of Fallot. To be published.
23. Sodi-Pallares, D., Portillo, B., Cisneros, F., De La Cruz, M. V. and Acosta, A. R. Electrocardiography in infants and children. *Pediat. Clin. North America*, 5: 871, 1958.
24. Medrano, G. Quoted by Sodi-Pallares et al.[23]
25. Cabrera, C. E. and Monroy, J. R. Systolic and diastolic loading of the heart; electrocardiographic data. *Am. Heart J.*, 43: 669, 1952.
26. Sokolow, M. and Lyon, T. P. The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am. Heart J.*, 38: 273, 1949.

The Clinical Value of Vectorcardiography*

EDWARD W. HECKERT, M.D., WILLIAM R. COOK, M.D.† *and* SEYMOURE KRAUSE, M.D., F.A.C.C.

Philadelphia, Pennsylvania

THERE IS NO GENERAL agreement at this time as to the best method of taking vectorcardiograms; therefore, a statement relative to the clinical value of vectorcardiography may appear premature. Furthermore, interpretation of vectorcardiograms at this comparatively early stage of our experience will inevitably be subject to great variation. Kossmann[1] clearly described these problems as follows: "With such real technical and fundamental difficulties in recording vectorcardiograms, it would seem wise not to recommend any one method for the moment. There is some question whether a large clinical investigation with any method is really worth while, since the data thus collected may readily become obsolete. Previous experience with electrocardiographic methods may provide an answer. We have used the Einthoven method of leading for almost half a century. In that time, initially by laborious, empirical, and frustrating research, we have been able to learn enough to make electrocardiography the most valuable single laboratory aid used in clinical cardiology today. If we had waited all this time to be sure that the Einthoven triangle was not equilateral, something that was known even to Einthoven, medicine would have been denied a very useful diagnostic tool. Perhaps the same approach should be made to vectorcardiography, preferably by those intensely interested and with a certain minimal technical capability in the field."

Finding ourselves with precisely the same two qualifications as listed by Kossmann, we have reviewed our experiences with vectorcardiography, placing particular emphasis upon the determination of those conditions in which the procedure may be expected to provide the most useful clinical information. We have been guided in our interpretations by many publications dealing with vectorcardiography, the most comprehensive of which is a single volume by Grishman and Scherlis.[2] However, a considerable number of vectorcardiograms with atypical features is likely to be encountered. Accurate interpretation is also hampered by the paucity of correlative autopsy data in most of the published studies on vectorcardiography.

MATERIAL AND METHODS

Vectorcardiograms of 1,000 selected adult patients were compared with their electrocardiograms and correlated with additional clinical information. Postmortem studies were available for 110 of the 1,000 cases. The cube system of vectorcardiography[2] was employed in all cases, and the tetrahedron system[3] was used also in 477 cases. Equipment consisted of the Sanborn Vector Amplifier and Visoscope.

The clinical usefulness of the vectorcardiogram as compared with the electrocardiogram was graded numerically as follows and summarized in Table 1:

5. Vectorcardiogram was diagnostic of an abnormality whereas electrocardiogram was within normal limits.
4. The vectorcardiogram was diagnostic of an abnormality whereas the electrocardiogram was abnormal but nonspecific; vectorcardiogram provided additional significant information.
3. Vectorcardiogram and electrocardiogram were considered diagnostic with similar interpretations; vectorcardiogram provided no additional information.
2. Vectorcardiogram and electrocardiogram were suggestive but not diagnostic of an abnormality; vectorcardiogram provided no additional information.
1. Vectorcardiogram revealed presence of an abnormality but was nonspecific; electrocardiogram was diagnostic of an abnormality; vectorcardiogram provided less information than the electrocardiogram.
0. Vectorcardiogram was within normal limits and the electrocardiogram was diagnostic of an abnormality.

* From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

† Present address: The Denver Clinic, Denver, Colorado.

TABLE I

Comparison of Electrocardiograms and Vectorcardiograms in 1000 Cases

Primary Diagnosis	Rating* of Vectorcardiogram and Electrocardiogram						Total No. of Cases
	0	1	2	3	4	5	
Myocardial hypertrophy							
Left ventricular hypertrophy	..	1	5	34	4	...	44
Left ventricular hypertrophy with terminal conduction delay	...	1	8	3	...	...	12
Right ventricular hypertrophy	...	1	6	42	36	..	85
Combined left and right ventricular hypertrophy	.	..	5	...	17	...	22
Left atrial hypertrophy	...	...	..	4	9	...	13
Myocardial infarction							
Anterior	1	10	27	88	82	1	209
Anterior and inferior	...	...	...	22	18	...	40
Inferior (diaphragmatic)	...	1	4	34	32	...	71
Posterior	...	...	8	16	17	...	41
Lateral	...	...	...	10	...	...	10
High anterior	...	12	7	...	...	...	19
Other	...	...	7	1	2	...	10
Bundle branch block							
Right bundle branch block, complete	...	...	2	54	3	...	59
Right bundle branch block with atypical features	...	...	6	23	2	...	31
Right bundle branch block with myocardial infarct	...	...	...	16	2	...	18
Right bundle branch block, incomplete	...	...	1	4	3	...	8
Left bundle branch block	...	...	...	42	3	...	45
Miscellaneous							
Increased degree of anterior orientation of QRS	...	2	47	9	5	...	63
Abnormal direction of inscription in sagittal plane QRS (representing the only abnormality)	...	...	5	...	14	...	19
Pulmonary disease (without right ventricular hypertrophy)	...	1	22	6	4	.	33
Pericarditis and myxedema	..	...	1	3	3	...	7
Wolff-Parkinson-White syndrome	...	...	1	6	1	...	8
Abnormal S-T or T as only abnormality	...	1	13	13	2	...	29
Miscellaneous	...	...	38	17	6	...	61
Normal	...	...	15	31	...	...	46
Total	1	30	228	478	265	1	1003†

* See text for explanation of rating system.

† In three of the 1,000 vectorcardiograms studied, left atrial hypertrophy was diagnosed in addition to QRS abnormalities, giving a total of 1,003 interpretations for 1,000 vectorcardiograms.

In several cases it appeared that the vectorcardiogram was superior to the routine twelve lead electrocardiogram. However, when additional precordial leads were examined (for example, in right ventricular hypertrophy), abnormalities sometimes became more obvious in the electrocardiogram, producing greater similarity between the electrocardiographic and vectorcardiographic interpretations.

RESULTS

Comparison of Vectorcardiograms and Electrocardiograms: It is obvious that a great deal of emphasis cannot be placed upon the statistics in Table I due to the inconsistencies unavoidably introduced by observer variation in electrocardiographic and vectorcardiographic interpretation. These problems in electrocardiography are well described by Davies[4] who found significant disagreement among cardiologists interpreting the same group of one hundred electrocardiograms on two different occasions. Perhaps our findings demonstrate more clearly than anything else the degree of proficiency which can be achieved in vectorcardiographic interpretation in a relatively short time, inasmuch as the authors have had considerably more experience with electrocardiography than with vectorcardiography. Despite the difficulties mentioned, it is believed that certain trends are revealed by the data in Table I.

When the electrocardiogram is well within normal limits, there is little likelihood that the vectorcardiogram will provide a definite diagnosis of an abnormality.

In the group of 478 vectorcardiographic interpretations assigned a numerical grading of 3, indicative of complete agreement between the vectorcardiogram and electrocardiogram, vectorcardiograms were taken chiefly to establish the validity of our methods. With the remaining 525 vectorcardiographic interpretations, however, better correlation was obtained clinically or by autopsy with the vectorcardiogram than with the electrocardiogram in 266 cases (graded with values of 4 and 5), while in only thirty-one cases (groups 1 and 0) was the electrocardiogram considered to be of more value than the vectorcardiogram. Therefore, in our study the vectorcardiogram provided additional information of clinical value in approximately half of the 525 cases which had somewhat equivocal electrocardiographic findings.

Comparison of Cube and Tetrahedron Systems: Table II indicates the comparative value of the cube and tetrahedron systems in various conditions in our series. In 477 cases in which both systems were employed, the tetrahedron system of vectorcardiography was considered to be

more valuable in sixty-three cases, while the cube system seemed to be more helpful in forty-seven instances. In the remaining 367 vectorcardiograms both systems provided similar information. However, we do not wish to imply that the tetrahedron system is superior to the cube system in the majority of cases. This apparent superiority of the tetrahedron system is probably the result of our practice of utilizing it, for the most part, only for the clarification of certain specific electrocardiographic findings. Both cube and tetrahedron systems were employed routinely in our first 200 cases. A preliminary review of our results at that point suggested that the tetrahedron was likely to provide more information than the cube chiefly in certain conditions. As a result, the tetrahedron has been used by us more recently only when the electrocardiogram suggests those diagnoses in which we expect it to provide more definite information than the cube system, thereby weighting the results in Table II in favor of the tetrahedron.

As suggested by the findings in Table II we have found the tetrahedron system more helpful in the following conditions: right ventricular hypertrophy, combined left and right ventricular hypertrophy, inferior (diaphragmatic) myocardial infarction and true posterior wall (posterobasal) myocardial infarction. We have also used the tetrahedron along with the cube system when electrocardiographic findings were interpreted as borderline abnormal or nonspecific. We have found the tetrahedron less useful than the cube system in bundle branch blocks, left ventricular hypertrophy, and anterior myocardial infarction. Gelfand et al.,[5] in a study of forty-two cases of right ventricular hypertrophy, using both vectorcardiographic systems, also concluded that the tetrahedron system was more sensitive than the cube in diagnosing milder degrees of right ventricular hypertrophy. Schaffer et al.[6] discussed "eccentricity" as a cause for differences between the vectorcardiograms registered by these two systems and predicted closer resemblance between findings in the anterior precordial leads and the cube system but better correlation between the posterior chest leads and the tetrahedron system. These views are supported for the most part by our findings as presented in Table II.

TABLE II

Comparison of Cube and Tetrahedron Systems of Vectorcardiography in 477 Cases

Diagnosis	Comparison of Systems			Total No. of Cases
	Tetrahedron better	Systems equal	Cube better	
Myocardial hypertrophy				
Left ventricular hypertrophy	...	7	6	13
Right ventricular hypertrophy	23	39	9	71
Combined left and right ventricular hypertrophy	11	8	2	21
Left atrial hypertrophy	1	1	1	3
Myocardial infarction				
Anterior	1	52	10	63
Anterolateral	1	4	...	5
High anterior	1	...	...	1
Inferior (diaphragmatic)	7	36	1	44
Posterior	4	22	2	28
Miscellaneous	2	7	...	9
Bundle branch block				
Right bundle branch block	...	34	5	39
Right bundle branch block with atypical features	1	23	1	25
Left bundle branch block	...	2	8	10
Miscellaneous				
Increased degree of anterior orientation of QRS	4	43	...	47
Abnormal direction of inscription in sagittal plane QRS (representing the only abnormality)	5	13	...	18
Pulmonary disease (without right ventricular hypertrophy)	2	18	...	20
Wolff-Parkinson-White syndrome	...	7	...	7
Miscellaneous	...	30	...	30
Normal	...	21	2	23
Total	63	367	47	477

COMMENTS

Examination of the data in Table I suggests that vectorcardiographic abnormalities reflected in the anteroposterior cardiac vectors were responsible for superiority of the vectorcardiogram over the electrocardiogram in a significant number of cases. Anterior orientation of certain portions of the QRS loop is important in the diagnosis of right ventricular hypertrophy, posterior myocardial infarction and right bundle branch block; posterior displacement of the QRS vectors is characteristic of left ventricular hypertrophy, anterior myocardial infarction and left bundle branch block. By contrast, myocardial infarcts limited to the lateral wall of the left ventricle cause vectors to be displaced toward the right, producing abnormalities more readily detected in the extremity and left precordial leads of the electrocardiogram.

In a group of our cases studied at autopsy, the previously described vectorcardiographic designation of "left ventricular hypertrophy with terminal conduction delay"[7] was noted to include a heterogeneous group of conditions including complete right bundle branch block with right ventricular hypertrophy, complete right bundle branch block associated with extensive anterolateral myocardial infarction, combined left and right ventricular hypertrophy of the idiopathic type or associated with arteriosclerotic heart disease, and brown atrophy of the myocardium. Left ventricular hypertrophy, therefore, was not a consistent feature of the cases with these vectorcardiographic findings.

Vectorcardiograms were interpreted as incomplete right bundle branch block when they displayed the features of complete right bundle branch block except for lesser degrees of conduction delay, producing a QRS duration of less than 0.12 second. Right ventricular hypertrophy was noted much more frequently than incomplete right bundle branch block in our series of vectorcardiograms. Although incomplete right bundle branch block may have been an unrecognized concomitant finding in some of our cases of right ventricular hypertrophy, vectorcardiograms interpreted as right ventricular hypertrophy have correlated well with available clinical and autopsy data.

Increased degree of anterior orientation of the QRS loop was a consistent finding in a small group of cases with either pericarditis or myxedema. Abnormalities of the S-T segment, particularly in acute myocardial infarction and acute pericarditis, were more marked in the precordial leads of the electrocardiogram than in the vectorcardiogram, presumably due to proximity of the precordial electrodes to the heart.

Although the search for the ideal system of vectorcardiography continues, we have found both the cube and tetrahedron systems a useful supplement to the twelve lead electrocardiogram.

Summary

1. Vectorcardiograms of 1,000 adult patients were studied and correlated with clinical data. Autopsy findings were also available in 11 per cent of the group.

2. The cube system was used in all cases, and the tetrahedron system of vectorcardiography was also employed in 477. The tetrahedron system usually revealed abnormalities better than the cube system in right ventricular hypertrophy, combined left and right ventricular hypertrophy, inferior myocardial infarction and posterior myocardial infarction. The cube system, on the other hand, was generally more helpful than the tetrahedron in cases of anterior myocardial infarction, left ventricular hypertrophy, left bundle branch block and right bundle branch block.

3. The vectorcardiogram provided additional and more decisive information in about half of 525 patients with somewhat equivocal electrocardiographic findings; the electrocardiogram revealed abnormalities better than the vectorcardiogram in only 6 per cent of the same group of cases. However, the vectorcardiogram and the electrocardiogram were interpreted similarly in the majority of the 1,000 cases. The vectorcardiogram was extremely unlikely to be diagnostic of an abnormality when the electrocardiogram was well within normal limits.

4. The vectorcardiogram offered additional help in the diagnosis of right ventricular hypertrophy, combined left and right ventricular hypertrophy, right bundle branch block and myocardial infarction in various locations with the exception of lateral or high anterior infarcts.

Acknowledgment

We wish to thank Mr. John Narvin and Mr. Barnett Long for their extensive technical assistance.

References

1. Kossmann, C. E. The electrocardiogram and vectorcardiogram in coronary heart disease. *J. Chronic Dis.*, 4: 458, 1956.
2. Grishman, A. and Scherlis, L. Spatial Vectorcardiography. Philadelphia, 1952. W. B. Saunders.
3. Wilson, F. N., Johnston, F. D. and Kossmann, C. E. The substitution of a tetrahedron for the Einthoven triangle. *Am. Heart J.*, 33: 594, 1947.
4. Davies, L. G. Observer variation in reports on electrocardiograms. *Brit. Heart J.*, 20: 153, 1958.
5. Gelfand, D., Urbach, J. R., Bellet, S. and Allison, W. Right ventricular hypertrophy. A study of the QRS loop of the spatial vectorcardiogram employing the cube and tetrahedron coordinates. *Cardiologia*, 26: 228, 1955.
6. Schaffer, A. I., Bergmann, P. G., Boyd, L. J., Mirkinson, A. and Beinfield, W. H. Eccentricity as a cause for the difference between the vectorcardiograms registered by the cube and tetrahedral systems. *Am. Heart J.*, 45: 448, 1953.
7. Wachtel, F. W., Lamelas, M., Grishman, A. and Donoso, E. The vectorcardiographic and electrocardiographic appearance of left ventricular hypertrophy with conduction delay. *J. Mt. Sinai Hosp.*, 23: 157, 1956.

The Electrocardiogram in Marfan's Syndrome*

DORRANCE BOWERS, M.D., M.S.(MED.), F.R.C.P.(C)
Kelowna, B. C., Canada

A WIDE variety of electrocardiographic abnormalties has been reported in patients with Marfan's syndrome (Table I). Some of these electrocardiographic abnormalities undoubtedly have stemmed from fortuitously associated cardiovascular diseases, such as rheumatic or syphilitic heart disease (Table II). The remaining electrocardiographic abnormalities have presumably resulted from those disorders of the cardiovascular system which appear to support the current concept of Marfan's syndrome as a diffuse disorder of connective tissues.[10] To date, three types of cardiovascular disease in this latter category have been recognized (Table II). The most impressive of these is a degenerative process involving the aorta or pulmonary artery, and giving rise to dilatation of these vessels with, at times, the formation of saccular or dissecting aneurysms.[11] A second type of cardiovascular disease with an apparent predilection for patients with Marfan's syndrome is diffuse myocardial hypertrophy and fibrosis, recently referred to by van Buchem[12] as "arachnodactyly heart." Third, the cardiovascular complications of kyphoscoliosis and pectus excavatum occur not infrequently in patients with Marfan's syndrome.[14]

In studying the electrocardiograms of fifty-five patients with Marfan's syndrome, I have been impressed by the high incidence of electrocardiographic abnormalities, by the influence of age and sex on the incidence of these abnormalities and by certain relationships between the abnormal electrocardiographic patterns and the state of the cardiovascular system in these patients. These observations are presented and discussed in this paper.

MATERIALS AND METHODS

Sixty-three electrocardiograms from fifty-five Canadian patients with Marfan's syndrome (Table III) served as the basis of this study. Many of these patients had been examined in teaching hospitals; the criteria for the diagnosis of Marfan's syndrome in these patients were not always known to me, and these diagnoses may reasonably be questioned; for example, the patient (E. M.) from whom electrocardiogram 18 was obtained is reported[6] not to have had dislocated ocular lenses, and the patient (S. K.) from whom electrocardiogram 19 was obtained is reported[22] to have had questionable arachnodactyly; nevertheless, these patients are probably representative of those who, in hospitals with enlightened medical staffs, are currently being diagnosed as having Marfan's syndrome. A total of sixteen electrocardiograms were obtained by me from sixteen patients; all these patients (with the exception of the patient [W. U.] from whom tracing 41 was obtained) had dislocated ocular lenses, the "hallmark" of Marfan's syndrome.[10]

Of fifty-five patients fourteen were members of the S. family.[13,26]

All tracings were taken on standard electrocardiographs. A total of 617 leads were recorded in the sixty-three tracings.

The results to be presented are derived from my interpretation of the tracings. Generally accepted diagnostic criteria were employed. Two criteria[29] were required for the electrocardiographic diagnosis of left ventricular hypertrophy: (1) SV_1 plus RV_5 greater than 35 mm., and (2) S-T segment depression or T wave inversion in leads V_5 or V_6.

RESULTS

1. Electrocardiographic Position of the Heart: The P wave was upright in standard lead I in every electrocardiogram except for tracings 45b and 50 in which the P waves were absent because of auricular fibrillation. In every electrocardiogram in which lead aVF was recorded, P in aVF was upright, with the exceptions of tracings 5b, 35, 41 and 44 in which it was either flat or diphasic, and of tracings 45b and 50, again because of auricular fibrillation.

* From the Knox Clinic, Kelowna, British Columbia, Canada.
This study was supported in part by a grant from the British Columbia Heart Foundation.

TABLE I
Electrocardiographic Patterns Reported in Patients with Marfan's Syndrome

Electrocardiographic Diagnosis	Author
Normal tracing	Marks and Gerson[1]
Ectopic sinus pacemaker	McKusick[2]
First degree atrioventricular block	Weiss, Thacker and Parmley[3]
Complete heart block	Sinclair[4]
Paroxysmal auricular tachycardia	McKusick[2]
Auricular fibrillation	Whitfield, Arnott and Stafford[5]
Left bundle branch block	McKusick[2]
Right bundle branch block	McKusick[2]
Left ventricular hypertrophy	Fay, Horlick, Merriman and Nanson[6]
Right ventricular hypertrophy	Golden and Lakin[7]
Left axis deviation	Steinberg, Mangiardi and Noble[8] (two cases)
Right axis deviation	Griffin and Koman[9]

TABLE II
Cardiovascular Abnormalities Associated with Marfan's Syndrome

A. Coincidental
   For example: syphilitic, rheumatic and ? congenital heart diseases
B. Intrinsic
   As a part of a diffuse disorder of connective tissue
   1. Cystic medial necrosis of the larger arteries resulting in "idiopathic" dilatation of the pulmonary artery, aortic valvular insufficiency, aneurysms of the sinuses of Valsalva, or saccular and dissecting aortic aneurysms
   2. Diffuse myocardial hypertrophy and fibrosis, so-called "arachnodactyly heart"
   3. Resulting from kyphoscoliosis and chest wall deformities

In most of the electrocardiograms the QRS axis was directed downward and to the left in the frontal plane (Table IV). The data suggested that counterclockwise rotation of the

TABLE III
Electrocardiograms from Patients with Marfan's Syndrome

ECG No.	Patient's Initials	Previous Reference	Age of Patient and Date ECG Taken	Source of ECG
1a	J. C.	V 16 S. family[13]	34 (Feb. 9, 57)	Author
1b	J. C.	V 16 S. family[13]	36 (Apr. 16, 59)	St. Joseph's Hosp.[14]
2a	P. K.	...	8 (Oct. 8, 57)	Vancouver General Hosp.[15]
2b	P. K.	...	10 (Oct. 7, 59)	Author
3	G. McD.	VI 9 S. family[13]	11	Author
4	H. McD.	V 17 S. family[13]	34	Author
5a	M. McK.	...	2 (Nov. 26, 51)	Vancouver General Hosp.[15]
5b	M. McK.	...	8 (Feb. 12, 58)	Vancouver General Hosp.[15]
5c	M. McK.	...	9 (Dec. 8, 58)	Vancouver General Hosp.[15]
6	R. O.	...	8	Author
7a	G. T.	...	17 (Apr. 20, 57)	Kingston General Hosp.[16]
7b	G. T.	...	19 (Oct. 14, 58)	Kingston General Hosp.[16]
8	L. P.	...	17	Royal Victoria Hosp.[17]
9	M. M.	...	25	Royal Victoria Hosp.[17]
10	E. M.	...	10	Victoria Hosp.[18]
11	L. K.	...	1	University of Alberta Hosp.[19]
12	M. G.	...	5	University of Alberta Hosp.[19]
13a	N. C.	V 15 S. family[13]	32 (June 26, 53)	Toronto General Hosp.[20]
13b	N. C.	V 15 S. family[13]	35 (Apr. 10, 56)	University of Alberta Hosp.[19]
13c	N. C.	V 15 S. family[13]	35 (May 26, 56)	Toronto General Hosp.[20]
14	S. W.	...	26	University of Alberta Hosp.[19]
15	N. H.	...	15	University of Alberta Hosp.[19]
16	Baby D.	...	7 days	University Hosp.[21]
17	D. L.	...	18	University Hosp.[21]
18	E. M.	Fay et al.[6]	30	University Hosp.[21]
19	S. K.	Manitoba Med. Rev.[22]	5	Children's Hosp.[23]
20	A. B.	...	10	Victoria Hosp.[18]
21	S. H.	...	18	Victoria Hosp.[18]
22	D. B.	...	15	Vancouver General Hosp.[15]
23	D. H.	...	16	Vancouver General Hosp.[15]

TABLE III *Continued*

ECG No.	Patient's Initials	Previous Reference	Age of Patient and Date ECG Taken	Source of ECG
24	D. H.	...	13	Author
25	H. M.	...	47	St. Michael's Hosp.[24]
26	L. E.	...	36	St. Michael's Hosp.[24]
27	M. B.	...	34	St. Michael's Hosp.[24]
28	N. F.	...	57	St. Michael's Hosp.[24]
29	M. M.	...	34	St. Michael's Hosp.[24]
30	A. K.	Baker et al.[25]	25	St. Michael's Hosp.[24]
31	C. S.	...	48	St. Michael's Hosp.[24]
32	V. A.	VI 8 S. family[13]	31	Author
33	A. S.	V 8 S. family[13]	49	Author
34	M. M.	VI 3 S. family[13]	37	Author
35	T. L.	VI 6 S. family[13]	25	Author
36	A. L.	VII 2 S. family[13]	5	Author
37	M. L.*	VII 3 S. family[26]	4	Author
38	P. L.*	VII 4 S. family[26]	3	Author
39	T. U.	IV 7 S. family[13]	68	Author
40	V. U.	V 24 S. family[13]	30	Author
41	W. U.†	V 23 S. family[26]	32	Author
42	E. McK.	...	40	Dr. D. C. Coleman[27]
43	G. B.	...	12	Hosp. for Sick Children[28]
44	W. H.	...	8	Hosp. for Sick Children[28]
45a	M. McG.	McKusick[10]	5 (July 18, 51)	Hosp. for Sick Children[28]
45b	M. McG.	McKusick[10]	10 (Nov. 9, 56)	Hosp. for Sick Children[28]
46	B. D.	...	9 months	Hosp. for Sick Children[28]
47	E. D.	...	13	Hosp. for Sick Children[28]
48	J. S.	...	15	Hosp. for Sick Children[28]
49	R. E.	...	14	Toronto General Hosp.[20]
50	W. H.	...	19	Toronto General Hosp.[20]
51	A. McL.	...	18	Toronto General Hosp.[20]
52	N. P.	...	22	Toronto General Hosp.[20]
53	R. R.	...	24	Toronto General Hosp.[20]
54	K. G.	...	25	Toronto General Hosp.[20]
55	T. D.	...	36	Toronto General Hosp.[20]

* M. L. and P. L. were considered not to have Marfan's syndrome when I first examined them in 1957.[13] When they were reexamined in 1959, both were found to have dislocated ocular lenses.[26] This observation has led me to believe that the lens dislocations are the result of an abiotrophic process affecting the suspensory ligaments of the lenses. † W. U. was classed among the "possibly affected cases, living" in 1957.[13] I examined him for the first time in 1959[26] (see case reports). He is now considered a "confirmed affected case" although he does not have ocular lens dislocations.

QRS axis in the frontal plane occurred in association with increasing age of the patients (Table IV). The left axis deviation in electrocardiogram 46 from a nine month old infant (B. D.) is a striking exception.

In most of the electrocardiograms the axis of the T wave was directed downward and to the left in the frontal plane (Table V). All tracings in which this axis was otherwise directed fell into the classification of abnormal tracings in the over-all interpretation.

2. Rhythm of the Heart: In every electrocardiogram, except 45b and 50, the heart rhythm was of sinus origin. Occasional auricular and ventricular premature beats were observed; these were not considered to be more common than might be expected in sixty-three electrocardiograms from fifty-five "normal" patients. Phasic sinus rhythm (sinus arrhythmia) was encountered commonly, particularly in the electrocardiograms from the younger patients.

In electrocardiogram 45b auricular fibrillation with an auricular rate of approximately 400/minute was present; the ventricular rate was approximately 60/minute. In electrocardiogram 50 also, auricular fibrillation was present, the auricular rate being approximately 425/minute and the ventricular rate approximately 160/minute.

TABLE IV

The QRS Axis in the Frontal Plane

On the Basis of the Positive and Negative QRS Deflections in Leads I and aVF, the Electrocardiograms Have Been Divided into Four Categories

QRS Deflections	R_1 Greater Than S_1	S_1 Greater Than R_1
R_{aVF} greater than S_{aVF}*	Axis between 0° and +90°	Axis between +90° and +180°
	1a, 1b, 2a, 3, 4, 5b, 5c, 9, 12, 14, 17, 22, 23 25, 26, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 44, 45a, 45b, 49, 50, 51, 52, 55	11, 15, 43, 47, 48, 54
	Median age, 25 years†	Median age, 13 years†
S_{aVF} greater than R_{aVF}*	Axis between 0° and −90°	Axis between +180° and −90°
	10, 13a, 13b, 13c, 18, 29, 39, 46	16
	Median age, 32 years†	Age, newborn

* aVF was not recorded in tracings 2b, 5a, 6, 7a, 7b, 8, 19, 20, 21, 24 and 53.

† Throughout this paper, in calculating median ages, the following procedure was employed for those patients represented by more than one electrocardiogram; the patient's age at the time of the most recent electrocardiogram was used, for example, the patient from whom tracings 13a, 13b and 13c were obtained was counted only once, at the age when his most recent electrocardiogram was taken, i.e., thirty-five years (Table III).

3. Conduction Disturbances: There were no examples of atrioventricular block in this series of electrocardiograms* except for the two tracings in which auricular fibrillation was present.

Incomplete right bundle branch block (that is, a secondary R deflection in lead V_1 with a QRS duration of less than 0.12 second) was present in seven electrocardiograms. These tracings were obtained from patients ranging in age from one to eighteen years.

* McKusick[10] has concluded that prolongation of the P-R interval occurs commonly in the electrocardiograms of patients with Marfan's syndrome.

TABLE V

The T Axis in the Frontal Plane

On the Basis of the Polarity of the T Deflections in Leads I and aVF, the Electrocardiograms Have Been Divided into Four Categories

T waves	Upright T_1	Inverted T_1‡
Upright T_{aVF}*	Axis between 0° and +90°	Axis between +90° and +180°
	3, 5b, 5c, 9, 10, 11, 15, 16, 17, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 42, 43, 44, 46, 47, 49, 51, 55	13b, 13c, 18
Inverted T_{aVF}†	Axis between 0° and −90°	Axis between +180° and −90°
	1a, 1b, 2a, 12, 41, 45b, 50, 54	14, 52

* T_{aVF} was flat or diphasic in tracings 4, 38, 45a and 48.

† aVF was not recorded in tracings 2b, 5a, 6, 7a, 7b, 8, 19, 20, 21, 24 and 53.

‡ T_1 was flat in tracing 13a.

Complete right bundle branch block was present in electrocardiogram 39 (Fig. 1).

There were no examples of left bundle branch or peri-infarction block.

4. Electrocardiographic Patterns: Forty-one tracings from forty-one patients were considered normal (electrocardiograms 3, 4, 5a, 6, 7a, 8, 9, 10, 11, 15, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 40, 42, 43, 44, 47, 48, 49, 51, 53 and 55). Electrocardiograms 2b and 45a were considered of equivocal diagnostic significance.

Twenty tracings from sixteen patients were considered abnormal (electrocardiograms 1a, 1b, 2a, 5b, 5c, 7b, 12, 13a, 13b, 13c, 14, 18, 31, 39, 41, 45b, 46, 50, 52 and 54) (Table VI). Electrocardiograms 1a, 1b, 5c and 13a had T wave abnormalities in leads I, V_4, V_5 or V_6. Electrocardiograms 2a, 12, 13a, 45b, 50, 52 and 54 (Fig. 2) had S-T segment depression or T wave inversion in leads II, III and aVF.

The electrocardiographic pattern of left ventricular hypertrophy was the single most common abnormal pattern, occurring in nine trac-

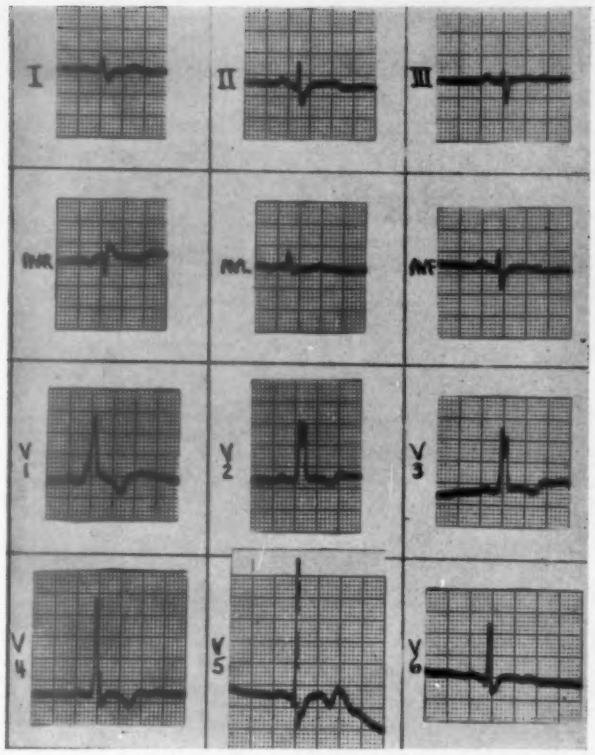


FIG. 1. Electrocardiogram 39. This tracing, showing the pattern of complete right bundle branch block, was obtained from a sixty-eight-year old male patient (T. U.) with Marfan's syndrome, member IV 7 of the S. family[18] (Fig. 3). (Electrocardiogram by the author.)

ings from eight patients. It is interesting that all electrocardiograms showing this pattern were obtained from male patients. None of the electrocardiograms suggested the diagnosis of old or recent myocardial infarction.

5. Associations between the Abnormal Electrocardiographic Patterns and the Age and Sex of the Patients: Table VII shows the percentage incidence of electrocardiographic abnormalities for each of two groups of patients; those twenty years of age or younger, and those above the age of twenty-one years. There is some evidence, summarized in a tetrachoric r 0.24, that an association between aging and electrocardiographic abnormalities is present.

Table VIII shows the percentage incidence of electrocardiographic abnormalities according to sex. It would appear that, in this group of patients with Marfan's syndrome, a greater tendency to have abnormal electrocardiograms occurs in male than in female patients (tetrachoric r, 0.48). It should be pointed out, however, that the median age of the male patients was twenty-two years and that of the females, fifteen years.

TABLE VI
Abnormal Electrocardiographic Patterns

Abnormal Patterns	Electrocardiograms	No. and Sex of Patients
T wave abnormalities in leads I, V_4, V_5 or V_6	1a, 1b, 5c, 13a	3 M:F = 3:0
S-T segment or T wave abnormalities in leads II, III and aVF	2a, 12, 13a, 45b, 50, 52, 54 Median age of patients, 17 yr.	7 M:F = 4:3
Left axis deviation in infancy	46	1
Auricular fibrillation	45b, 50 Ages of patients 10 and 19 yr.	2 M:F = 1:1
Left ventricular hypertrophy	5b, 7b, 13b, 13c, 14, 18, 31, 41, 52 Median age of patients, 28 yr.	8 M:F = 8:0
Complete right bundle branch block	39	1 Male
Totals*	20	16 M:F = 12:4

* These total figures are *not* the sums of the figures in the columns because some electrocardiograms and some patients are referred to more than once in the table.

It is interesting that the abnormal electrocardiograms in the male patients tended to occur in the older male, while the abnormal electrocardiograms in the female patients tended to occur in the younger female (Tables IX and X). Electrocardiographic abnormalities appeared equally commonly in male and female patients below the age of twenty years, and occurred exclusively in male patients after the age of twenty-one years.

6. Relationships between the Electrocardiographic Patterns and the Clinical Condition of the Patients: Brief case reports have been selected to illustrate the presence of both positive and negative correlations between the electrocardiographic patterns and the cardiovascular abnormalities in these patients. The fact that a normal electrocardiogram does not exclude serious disorders of the cardiovascular system is clearly

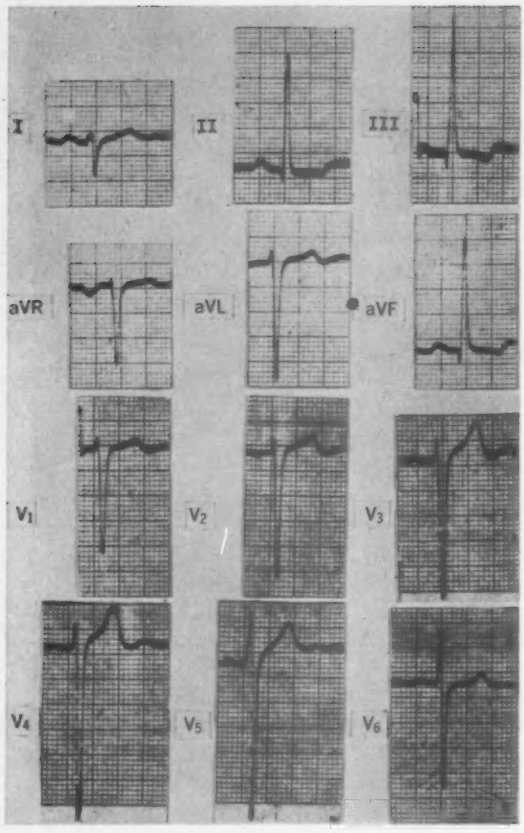


FIG. 2. Electrocardiogram 54. This tracing was obtained from a twenty-five year old male patient (K. G.) with Marfan's syndrome studied at the Toronto General Hospital.[20] It shows the pattern of right axis deviation, as well as abnormal ST segment depressions and inverted T waves in leads II, III and aVF.

shown by the data concerning patients A. K. and G. B. A positive correlation between abnormal electrocardiograms and the presence of cardiovascular disease is illustrated by the notes concerning patients J. C., G. T., N. C., E. M., T. U., W. U. and M. McG.

Patient A. K. A detailed report concerning this patient was published by Baker, Wilson and Woods.[25] When the patient was at the age of twenty-five, a dissecting aneurysm of the descending thoracic aorta developed following obstetric confinement. She did not have a family history of Marfan's syndrome, and her ocular lenses were said not to be dislocated. She was tall and thin and had long spidery extremities. Her electrocardiogram (30) was within normal limits.

Patient G. B. Data concerning this boy, who was twelve years old in 1955, were supplied by Dr. R. D. Rowe.[28] This patient had club feet, pectus excavatum, a cleft palate and variable ptosis with a lack of normal retinal correspondence. His electrocardiogram (43) showed incomplete right bundle branch block and right axis deviation; it was considered within normal limits. By selective angiocardiography an aneurysm of the proximal portion of the pulmonary artery was demonstrated.

TABLE VII
Incidence of Electrocardiographic Abnormalties According to Age

Interpretation of Electrocardiogram	Percentage Incidence of ECG Abnormalties According to Age	
	Twenty Years of Age or Younger	Older than Twenty-one Years
Normal	77	64
Abnormal	23	36

Tetrachoric r is 0.24.

TABLE VIII
Incidence of Electrocardiographic Abnormalities According to Sex

Interpretation of Electrocardiogram	Percentage Incidence of ECG Abnormalities According to Sex	
	Male	Female
Normal	61	83
Abnormal	39	17

Tetrachoric r is 0.48.

Patient J. C. This man, now thirty-seven years of age, was previously reported[13] as member V 16 of the S. family. He has the classic physical characteristics of Marfan's syndrome, the dolichochephalic skull, high arched palate and gracile extremities. He had had bilateral lens dislocations. As a complication of repeated ophthalmologic surgery, his left eye had required enucleation; limited vision remains in his right eye.

For the past three years, he has had recurrent severe pains in his neck, chest and abdomen. Repeated physical examination and routine radiographic studies have been unrewarding in establishing the cause of these pains. Repeated serum glutamic oxalacetic transaminase determinations have been within normal limits.[14] His electrocardiograms (1a, 1b) show persistent nonspecific T wave abnormalities. It has been suspected that the pains are caused by minor aortic dissections.

Patient G. T. The data concerning this patient were made available by the Medical Records Department of the Kingston General Hospital.[16] When he was first examined at the age of seventeen in April 1957, he had the skeletal and ocular features typical of Marfan's syndrome. At that time his

TABLE IX

Influence of Sex and Age on the Incidence of Abnormal Electrocardiographic Patterns in Fifty-Five Patients with Marfan's Syndrome

No. of Patients	Male	Female
Number of patients (B)	31	24
Median age (years)	22	15
Number of patients with abnormal electrocardiograms (A)	12	4
Median age (years)	28	7
A/B as a percentage	39	17

TABLE X

Influence of Age and Sex on the Incidence of Abnormal Electrocardiographic Patterns in Fifty-Five Patients with Marfan's Syndrome

No. of Patients	Patients Twenty Years of Age or Younger	Patients Older than Twenty-one Years
Total number of patients (C)	30	25
Number of male patients (D)	15	16
Number of patients with abnormal electrocardiograms (B)	7	9
Number of male patients with abnormal electrocardiograms (A)	3	9
A/B as a percentage	43	100
B/C as a percentage	23	36
A/D as a percentage (male patients)	20	56
B-A/C-D as a percentage (female patients)	27	0

electrocardiogram (7a) was normal. Radiologic examination indicated that the aorta was somewhat elongated and slightly dilated.

On September 18, 1958, moderately severe pain developed initially in the throat, but later in the anterior and posterior neck and in the left shoulder. Following this, he was observed to have a grade 3 aortic diastolic murmur, and the blood pressure was 136/30 mm. Hg; previously, it had been 124/70 mm. Hg. Radiologic examination revealed no further widening of the aorta; the heart shadow was wider than at the time of his previous examination.

FIG. 3. This sixty-eight year old man (T. U.) has previously been reported[13] as member IV 7 of the S. family. Note the thick lenses in his spectacles to correct for the gross displacement of his ocular lenses; note also the dolichocephaly, arachnodactyly, kyphosis and pectus excavatum. His electrocardiogram is reproduced in Figure 1.

His electrocardiogram (7b) then presented the pattern indicative of left ventricular hypertrophy.

Patient N. C. This man was previously reported[13] as member V 15 of the S. family. The data concerning him were made available by the Medical Records Departments of the Toronto General Hospital[20] and of the University of Alberta Hospital.[19]

He had had bilateral ocular lens dislocations and had required extraction of the lens from the left eye following the development of secondary glaucoma. He was dolichocephalic and had kyphoscoliosis of the thoracic spine; he had long slender fingers and toes. The following evidence was interpreted to indicate that he had moderately severe aortic valvular insufficiency: blood pressure 120/40 mm. Hg; a grade 3 left parasternal and apical diastolic murmur; and left ventricular hypertrophy on both fluoroscopic and electrocardiographic (13b and 13c) examination.

Routine serologic tests for syphilis repeatedly were positive as was a Treponema pallidum immobilization test.

He died at his home in 1956 at the age of thirty-five apparently as a result of intractable cardiac failure. No postmortem examination was performed.

Patient E. M. A detailed report concerning this thirty year old male patient has been published by Fay, Horlick, Merriman and Nanson.[6] He had a saccular aneurysm of the ascending aorta. His

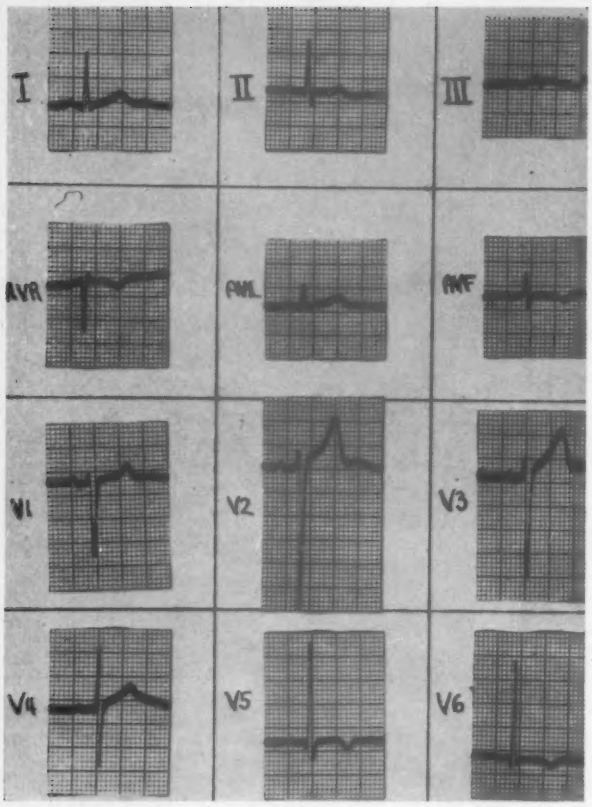


FIG. 4. Electrocardiogram 41. This electrocardiogram was obtained from a thirty-two year old male patient (W. U.) with Marfan's syndrome, member V 23 of the S. family.[26] This tracing illustrates the pattern of left ventricular hypertrophy.

electrocardiogram (18) showed the typical pattern indicative of left ventricular hypertrophy. The patient died following surgical repair of the aneurysm. At necropsy cystic medionecrosis of the aorta was demonstrated histologically.

Patient T. U. This patient, now sixty-eight years of age, was previously reported[13] as member IV 7 of the S. family. He has bilateral dislocations of the ocular lenses, dolichocephaly, a high arched palate, long spidery extremities, marked dorsal kyphosis and a funnel-chest deformity. Many of these abnormalities are illustrated in Figure 3.

This man is now prevented from working by easily induced breathlessness. He has no chest pain and no evidence of fluid retention. Blood pressure is 160/80 mm. Hg; he has no murmurs. His electrocardiogram (39) shows complete right bundle branch block (Fig. 1).

Patient W. U. This man, now thirty-two years of age, member V 23 of the S. family, has been examined[26] since the first report[13] of the S. family was published. Although he has a tall thin head and a high narrow palate, he is stockily built and his extremities appear normal. He is myopic but there is no dislocation of his ocular lenses.

He has a grade 2 aortic diastolic murmur best heart along the left sternal border. Radiologic examination of his chest was not performed. His electrocardiogram (41) shows the pattern of left ventricular hypertrophy (Fig. 4).

Patient M. McG. Data concerning this patient who died at the Hospital for Sick Children in Toronto at the age of ten years were supplied by Dr. R. D. Rowe.[28] She had dislocated ocular lenses, pectus excavatum and scoliosis. Her photograph has been published by McKusick[10] (his Fig. 4E). She died as a result of mitral insufficiency and congestive heart failure. Her electrocardiogram (45a) when she was five years old was of debatable significance. An electrocardiogram (45b), made shortly before her death, showed auricular fibrillation and S-T segment depression and T wave inversion in leads II, III and aVF. "Autopsy revealed changes of a typical nature in aorta, pulmonary artery, and mitral areas."[28]

COMMENTS

The results of any study of electrocardiograms from a group of patients with Marfan's syndrome obviously will be influenced by the selection of the patients. The greater the number of patients studied, the greater the likelihood that the sample population will be representative of all patients with Marfan's syndrome. Several facts suggest that the sample of patients in this study (despite the relatively large number) is not representative of all patients with Marfan's syndrome. First, this group of patients is not equally weighted with male and female patients; it has been shown repeatedly that Marfan's syndrome is not a sex-linked abnormality. Second, the male patients in this series were older (median age, twenty-two years) than the female patients (median age, fifteen years); elsewhere, the author[13] has shown that, on the average in the S. family, female patients with Marfan's syndrome have lived longer than male patients with this disorder. Third, many of the patients in this investigation were hospitalized patients; presumably, hospitalized patients will have a higher incidence of electrocardiographic abnormalities than nonhospitalized patients. Fourth, all the patients in this study were Canadians; it may be that social, climatic or other environmental factors influence the nature or incidence of electrocardiographic abnormalities. Fifth, fourteen of the fifty-five patients belonged to a single family.[13,26] Finally, the criteria for the diagnosis of Marfan's syndrome in these patients have not been clearly defined and may not have been consistent. For these reasons, the results of this

study may be regarded only as interesting, certainly not as authoritative.

Electrical Axis: To my knowledge, no investigation of the anatomic position of the heart in patients with Marfan's syndrome has been published. In view of the skeletal abnormalities in patients with Marfan's syndrome—the tall, thin body build, the frequent kyphoscoliosis and the not uncommonly associated deformities of the anterior chest wall (Fig. 3)—the anatomic position of the heart in these patients might be expected to differ from the normal. Although there is no close correlation between the anatomic and the electrical positions of the heart,[30] it was considered important in this investigation to examine carefully the electrical position of the heart. The data revealed no evidence for a characteristically abnormal electrical position of the heart in these patients with Marfan's syndrome;* rather they indicated that abnormal electrical positions were frequently the results of coexistent cardiovascular abnormalities. The counterclockwise rotation of the QRS axis in the frontal plane occurring in association with increasing age of the patients in this study (Table IV) is an interesting phenomenon, and will be the subject of comment in a later paragraph.

Incidence of Abnormalities: The high incidence of electrocardiographic abnormalities in this group of young patients with Marfan's syndrome is impressive; sixteen of the fifty-five patients had abnormal electrocardiograms, the median age of the fifty-five patients being 18.5 years. This observation suggests that cardiovascular "complications" in Marfan's syndrome are not uncommon, particularly when it is remembered that some of the patients with normal electrocardiograms also have cardiovascular disorders. If electrocardiographic abnormalities occur in 29 per cent of all patients with Marfan's syndrome (the observed incidence in this study), it seems possible that cardiovascular disease may occur in as many as one-third of all patients with Marfan's syndrome. Tentative estimates of the incidence of cardiovascular disease resulting from Marfan's syndrome may be ventured. Lynas[33] observed that (in Northern Ireland) Marfan's syndrome occurred in one in 70,000 persons; if cardiovascular "complications" occur in one-third of patients with Marfan's syndrome, it may be extrapolated that there are in Canada approximately one hundred patients (and in the United States approximately 1,000 patients) with the cardiovascular "complications" of Marfan's syndrome.

Age: In this group of patients, the aging process seemed to be associated with a rising incidence of abnormal electrocardiograms; it was observed that the median age of the sixteen patients with abnormal electrocardiograms was 23.5 years, that is, higher than the median age of all the patients in the study (18.5 years), and that 23 per cent of patients twenty years of age or younger had abnormal electrocardiograms, while 36 per cent of patients older than twenty-one years had abnormal electrocardiograms (Table VII). The increasing incidence of electrocardiographic abnormalities in association with the aging process supports the prevailing concept of Marfan's syndrome as an abiotrophy of the cardiovascular system.

Sex Differences: The sex of the patients appeared, in this investigation, to influence the incidence of electrocardiographic abnormalities; abnormal tracings were found in 39 per cent of the male patients and 17 per cent of the female patients (Table VIII). The fact that the male patients were older (median age, twenty-two years) than the female patients (median age, fifteen years) is thought not to be the sole reason for the sex difference in the incidence of electrocardiographic abnormalities. It is interesting that the sex difference in the incidence of abnormal electrocardiograms should coincide with the long recognized sex difference[34] in the incidence of aortic dissections. (Recently, a sex difference has been reported in the incidence of aortic rupture induced by Lathyrus odoratus in immature rats.[35]) It is also of interest to relate the sex difference in the incidence of the abnormal electrocardiograms to previous observations in my studies[13,26] of Marfan's syndrome in the S. family, namely: (1) that the average age at death for male patients was lower than the corresponding age for female patients; (2) that affected male patients had a strikingly lower fertility rate than did the affected women;

* The papers by Gray[31] and by Elisberg[32] are of interest in reference to the electrical position of the heart in patients with chest deformities. Gray, in reviewing the electrocardiograms of nineteen patients with kyphoscoliosis, found no consistent electrical position of the heart; the tracings were almost equally divided among normal, left axis deviation, and right axis deviation patterns. Elisberg has published electrocardiograms from six patients with pectus excavatum; I have concluded from my examination of the electrocardiograms published by Elisberg that pectus excavatum is not associated with a uniformly abnormal electrical position of the heart.

and (3) that affected male patients had a record of meager productivity and frequently required social assistance. All these observations are consistent with the conclusion that the male patient with Marfan's syndrome is (on the average) more seriously handicapped than the female patient.

Left Ventricular Hypertrophy: The single most common abnormal electrocardiographic pattern in this study (Table VI) was the pattern indicative of left ventricular hypertrophy* (nine tracings from eight patients). Also, in four electrocardiograms (1a, 1b, 5c and 13a) from three patients, there were T wave abnormalities in leads I, V_4, V_5 or V_6 but $SV_1 + RV_5$ was less than 35 mm. It is possible that the abnormalities in these electrocardiograms resulted from early left ventricular hypertrophy because tracings 5b, 13b and 13c from two of these three patients did meet both diagnostic criteria for left ventricular hypertrophy. In this connection, Griep[38] commented: "On the basis of voltage criteria alone, it would appear that a patient could have left ventricular hypertrophy one day and not the next." The counterclockwise rotation of the QRS axis in the frontal plane in association with the aging process (Table IV) may also be an expression of increasing size of the left ventricle. The left ventricular hypertrophy patterns (Fig. 4) were thought to result from aortic valvular insufficiency (see clinical notes concerning patients N. C., G. T., W. U. and E. M.) probably due to dilatation of the aortic valve ring. It is striking that all the patients with electrocardiographic patterns diagnostic of left ventricular hypertrophy were men (Table VI).

S-T and T Abnormalities: The pattern of S-T segment depression or T wave inversion in leads II, III and aVF was the second most common abnormal electrocardiographic pattern in this study (seven tracings from seven patients) (Table VI). It was present in the two tracings (45b and 50) in which auricular fibrillation occurred. In two of these seven tracings (2a and 13a), there were T wave inversions only; in the remaining five tracings (12, 45b, 50, 52 and 54), there were S-T segment depressions as well as T wave inversions in leads II, III and aVF. In tracing 52 there was, in addition, S-T segment depression in lead V_5; this tracing was similar to those published by Miller and Pearson[39] (their Fig. 4) and by Griffin and Koman[9] (their Fig. 5A); possibly, this electrocardiographic pattern results from biventricular hypertrophy. In tracings 12, 45b, 50 and 54 (Fig. 2), which were similar to the tracing published by Golden and Lakin[7] (their Fig. 5), the configuration of the deflections in the left precordial leads was not remarkable; it was presumed that the electrocardiographic abnormalities in these four tracings, from two female and two male patients, resulted from right ventricular hypertrophy or digitalis medication or both.[40] Unfortunately, the data available were not sufficient to permit a detailed correlation between this pattern and the cardiovascular status of the patients from whom it was recorded.

Right Bundle Branch Block: The demonstration of incomplete right bundle branch block in seven patients and of complete right bundle branch block in one patient in this study deserves comment. In the past there have been numerous suggestions in the medical literature that atrial septal defects occur not infrequently in patients with Marfan's syndrome. It is generally agreed that incomplete or complete right bundle branch block are the characteristic findings in the electrocardiograms of patients with atrial septal defects. It might then be concluded that the conduction disturbances demonstrated in this investigation were the results of defects in the atrial septa of these patients. I suspect, for three reasons, that such a conclusion would probably be incorrect: (1) it is now believed[41] that atrial septal defects occur infrequently in patients with Marfan's syndrome; (2) the pattern of incomplete right bundle branch block occurs commonly in patients without heart or lung disease;[42] and (3) although complete data concerning the clinical or necropsy findings related to the cardiovascular system were not available to me for all the patients in this study, none was known to have an atrial septal defect. The observation by Elisberg[32] of R′ deflections in precordial lead V_1 in the electrocardiograms of four of six patients with pectus excavatum suggests a possible explanation for the same pattern observed in these patients with Marfan's syndrome.

It should be clearly understood that, in this investigation, no attempt has been made to exclude coincidental cardiovascular abnormalities as possible determinants of the electrocardiographic patterns. Also, possibly divergent interpretations of some of the electrocardiograms by other investigators[43] might have

* The fallibility of currently accepted criteria for the electrocardiographic diagnosis of left ventricular hypertrophy is recognized.[36–38]

resulted in different conclusions being drawn from these electrocardiograms. These two important considerations, the failure to exclude coincidental cardiovascular diseases and the subjectivity of electrocardiographic interpretation, together with the probability that the patients in this study are not representative of all patients with Marfan's syndrome, should not be forgotten in any evaluation of the conclusions from this study.

Summary and Conclusion

Sixty-three electrocardiograms from fifty-five Canadian patients (median age, 18.5 years) with Marfan's syndrome have been studied. Case histories of patients in whom cardiovascular disease was associated with electrocardiographic abnormalities have been presented, along with case histories of patients with serious cardiovascular abnormalities but without electrocardiographic abnormalities.

Thirty-nine per cent of male patients, 17 per cent of female patients, 23 per cent of patients twenty years of age or younger, and 36 per cent of patients older than twenty-one years had abnormal tracings.

The most common abnormal electrocardiographic pattern (nine tracings from eight patients) was the pattern of left ventricular hypertrophy; this pattern was found in tracings from male patients only. It was thought to reflect left ventricular hypertrophy due to aortic valvular insufficiency.

The second most common abnormal electrocardiographic pattern (found in tracings from four male and three female patients) consisted of S-T segment depression or T wave inversion in leads II, III and aVF. This pattern was thought to be a reflection of right ventricular or biventricular hypertrophy, or to be an effect of digitalis.

Auricular fibrillation was recorded in two electrocardiograms, incomplete right bundle branch block in seven and complete right bundle branch block in one. There were no other significant disturbances of rhythm or conduction.

From these observations it was concluded that in this group of patients Marfan's syndrome is an abiotrophic disorder of the cardiovascular system frequently associated with nonspecific electrocardiographic abnormalities.

Acknowledgment

The author is indebted to Dr. Henry Bowers for his assistance in the preparation of the manuscript.

Addendum

Further study[44] of the electrocardiographic pattern of S-T segment depression or T wave inversion in leads II, III and aVF in patients with Marfan's syndrome has indicated that this pattern may be associated with mitral valve deformity.

References

1. Marks, J. and Gerson, K. L. Importance of autopsies; an illustrative case. *J. A. M. A.*, 168: 1450, 1958.
2. McKusick, V. A. The cardiovascular aspects of Marfan's syndrome: a heritable disorder of connective tissue. *Circulation*, 11: 321, 1955.
3. Weiss, E., Thacker, C. W. and Parmley, W. E., Jr. Marfan's syndrome (arachnodactyly) in half brothers: a case report. *J. Indiana M. A.*, 49: 1411, 1956.
4. Sinclair, R. J. G. The Marfan syndrome. *Bull. Rheumat. Dis.*, 8: 153, 1958.
5. Whitfield, A. G. W., Arnott, W. M. and Stafford, J. L. "Myocarditis" and aortic hypoplasia in arachnodactyly. Report of case. *Lancet*, 1: 1387, 1951.
6. Fay, J. E., Horlick, L., Merriman, J. E. and Nanson, E. M. A case of Marfan's syndrome with an aneurysm at the ascending aorta, with physiologic, operative and postmortem studies. *Canad. M. A. J.*, 78: 862, 1958.
7. Golden, R. L. and Lakin, H. The forme fruste in Marfan's syndrome. *New England J. Med.*, 260: 797, 1959.
8. Steinberg, I., Mangiardi, J. L. and Noble, W. J. Aneurysmal dilatation of the aortic sinuses in Marfan's syndrome: angiocardiographic and cardiac catheterization studies in identical twins. *Circulation*, 16: 368, 1957.
9. Griffin, J. F. and Koman, G. M. Severe aortic insufficiency in Marfan's syndrome. *Ann. Int. Med.*, 48: 174, 1958.
10. McKusick, V. A. The Marfan syndrome. In: Heritable Disorders of Connective Tissue, chapt. 3, 1st ed., pp. 36–85; 2nd ed., pp. 42–134. St. Louis, 1956; 1960. C. V. Mosby Co.
11. Baer, R. W., Taussig, H. B. and Oppenheimer, E. H. Congenital aneurysmal dilatation of the aorta associated with arachnodactyly. *Bull. Johns Hopkins Hosp.*, 72: 309, 1943.
12. van Buchem, F. S. P. Arachnodactyly heart. *Circulation*, 20: 88, 1959.
13. Bowers, D. Marfan's syndrome and the Weill-Marchesani syndrome in the S. family. *Ann. Int. Med.*, 51: 1049, 1959.
14. Personal communication. Medical Records Department, St. Joseph's Hospital, Toronto, Ontario.
15. Personal communication. Medical Records Department, Vancouver General Hospital, Vancouver, British Columbia.
16. Personal communication. Medical Records Department, Kingston General Hospital, Kingston, Ontario.
17. Personal communication. Medical Records Department, Royal Victoria Hospital, Montreal, Quebec.

18. Personal communication. Medical Records Department, Victoria Hospital, London, Ontario.
19. Personal communication. Medical Records Department, University of Alberta Hospital, Edmonton, Alberta.
20. Personal communications. Medical Records Department and Dr. C. R. Burton, Toronto General Hospital, Toronto, Ontario.
21. Personal communication. Medical Records Department, University Hospital, Saskatoon, Saskatchewan.
22. Case presentation at Ward Rounds. Children's Hospital, Winnipeg. Case 2. Atypical Marfan's syndrome. *Manitoba M. Rev.*, 34: 412, 1954.
23. Personal communication. Medical Records Department, Children's Hospital, Winnipeg, Manitoba.
24. Personal communication. Medical Records Department, St. Michael's Hospital, Toronto, Ontario.
25. Baker, C. B., Wilson J. K. and Woods, J. M. Marfan's syndrome—a successful aortic homograft for a dissecting aneurysm of the thoracic aorta. *Canad. J. Surg.*, 1: 371, 1958.
26. Bowers, D. Marfan's syndrome: the S. family revisited. Unpublished data.
27. Personal communication. Dr. D. C. Coleman, Courtenay, British Columbia.
28. Personal communications. Medical Records Department and Dr. R. D. Rowe, Hospital for Sick Children, Toronto, Ontario.
29. Sokolow, M. and Lyon, T. P. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am. Heart J.*, 37: 161, 1949.
30. Wolff, L. Electrocardiography: Fundamentals and Clinical Application, 2nd ed., p. 342. Philadelphia 1956. W. B. Saunders Co.
31. Gray, F. D., Jr. Kyphoscoliosis and heart disease. *J. Chron. Dis.*, 4: 499, 1956.
32. Elisberg, E. I. Electrocardiographic changes associated with pectus excavatum. *Ann. Int. Med.*, 49: 130, 1958.
33. Lynas, M. A. Marfan's syndrome in Northern Ireland; an account of thirteen families. *Ann. Human Genet.*, 22: 310, 1958.
34. DeBakey, M. E. and Crawford, E. S. Surgical considerations of acquired diseases of the aorta and major peripheral arteries. II. Dissecting aneurysms of the aorta. *Mod. Concepts Cardiovas. Dis.*, 28: 563, 1959.
35. Wajda, I., Lehr, D. and Krukowsi, M. Sex difference in aortic rupture induced by Lathyrus odoratus in immature rats. *Fed. Proc.*, 16: 343, 1957.
36. Selzer, A., Ebnother, C. L., Packard, P., Stone, A. O. and Quinn, J. E. Reliability of electrocardiographic diagnosis of left ventricular hypertrophy. *Circulation*, 17: 255, 1958.
37. Allenstein, B. J. and Mori, H. Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison. *Circulation*, 21: 401, 1960.
38. Griep, A. H. Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy: a correlative study of 200 autopsied patients. *Circulation*, 20: 30, 1959.
39. Miller, R., Jr. and Pearson, R. J., Jr. Mitral insufficiency simulating aortic stenosis; report of an unusual manifestation of Marfan's syndrome. *New England J. Med.*, 260: 1210, 1959.
40. Barnes, A. R. Electrocardiographic Patterns: Their Diagnostic and Clinical Significance, p. 197. Springfield, Ill., 1940. Charles C Thomas Co.
41. McKusick, V. A. The genetic aspects of cardiovascular diseases. *Ann. Int. Med.*, 49: 556, 1958.
42. Heidel, W. Clinical and electrocardiographic findings in incomplete right bundle branch block. *Ztschr. Kreislaufforsch*, 48: 47, 1959. (Abstr. in: *Circulation*, 20: 460, 1959.)
43. Segal, H. N. The electrocardiogram and its interpretation: a study of reports by 20 physicians on a set of 100 electrocardiograms. *Canad. M. A. J.*, 82: 2, 1960.
44. Bowers, F. An electrocardiographic pattern associated with mitral valve deformity in Marfan's syndrome. *Circulation*, 23: 30, 1961.

Serum Glutamic Oxalacetic Transaminase Activity in Acute Coronary Thrombosis with Myocardial Infarction

Relation to Prognosis*

MARSH MCCALL, M.D., F.A.C.C., ARTHUR HERTZ, M.D., F.A.C.C., IRVING RAPPAPORT, M.D. *and* WILLIAM NELSON, PH.D.

New York, New York

INVESTIGATIONS BY LaDue, Wrøblewski and Karmen[1] showed that an increase in serum glutamic oxalacetic transaminase activity (SGO-T) occurs in acute myocardial infarction. These observations have been confirmed by others.[2–6] Agress and his co-workers[7] demonstrated at postmortem examination that the circumscribed area of myocardial infarction was grossly proportional to the SGO-T activity in the serum. Serum glutamic oxalacetic transaminase is not a specific enzyme for cardiac muscle, but is a mixture derived from several tissues; however, its rapid rise in the serum following acute transmural myocardial infarction has been a consistent finding. Patients in this investigation were admitted by ambulance within two to six hours following the onset of acute pain in the chest; therefore, it seemed appropriate to make a special study of the SGO-T activity with relation to the diagnosis, management and immediate prognosis.

MATERIALS AND METHODS

A diagnosis of acute transmural myocardial infarction was made in 186 admissions to the cardiovascular service. These patients had acute retrosternal pain and subsequently showed serial electrocardiographic changes associated with acute transmural myocardial infarction. Necropsy evidence of acute infarction was obtained in eighteen patients.

Twelve lead electrocardiograms were made on admission and daily thereafter for five days. Displacement of the RS-T segments, serial changes in the QRS-T complexes and abnormal Q waves were the criteria for the diagnosis of acute myocardial infarction.

Venous blood was drawn within two hours of admission and then daily for five days. Serum to be tested was refrigerated at 4° C. for from two to five days prior to estimation of SGO-T activity. In our laboratory we have noted that serum glutamic oxalacetic transaminase at high activity is stable for at least eight weeks at 4° C. With minor modification the method of Reitman and Frankel[8] was used. All determinations were made using 0.2 ml. of serum except when greatly increased enzyme activity required a 1:10 dilution. The enzyme system was allowed to react with the substrate for one hour at 37° C. at pH 7.5. Measurements were made on a Bausch and Lomb spectronic 20 colorimeter using an 11.67 mm. colorimeter tube at wavelength of 505 mμ. The per cent transmission was plotted against the concentration of pyruvate and recorded in SGO-T units per ml. of serum. One unit represents the formation of chromogenic material equivalent to one gamma of pyruvate. The SGO-T activity range was 15 to 55 units in normal adults as well as in adult patients with cardiac disease (American Heart Association Standard Classification I and II). The mean activity was 32.3 units with a standard deviation (S.D.) of 11.5 units.

OBSERVATIONS

Figure 1 shows the mean SGO-T activity in 186 patients during the first ninety-six hours. Curve R of Figure 1 represents the mean SGO-T activity of 150 patients who recovered. Curve R+ represents the mean activity plus two S.D. while curve R− represents the mean activity minus two S.D. In the recovery group, seventy-eight patients had a peak SGO-T level of less then twice normal values. These were permitted early ambulation. The remaining

* From the Departments of Medicine and Pathology, Beekman-Downtown Hospital, New York, New York.

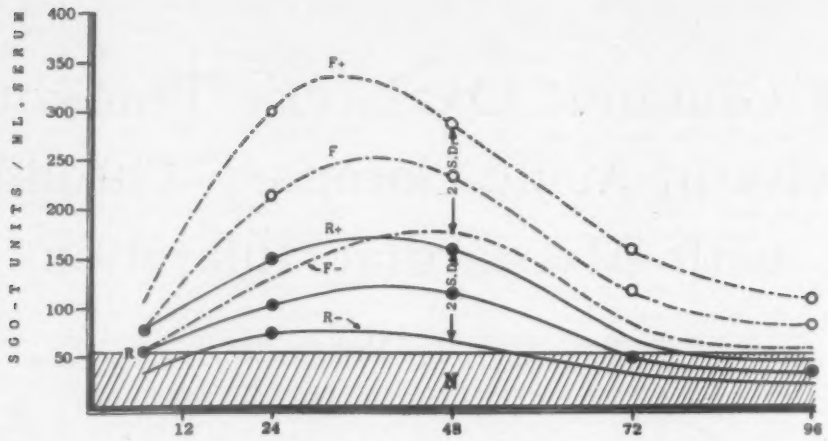


FIG. 1. Distribution of recoveries and fatalities in respect to SGO-T activity. R = mean curve of 150 patients who recovered. R+ = R plus two S.D. R− = R minus two S.D. F = mean curve of thirty-six fatalities. F+ = F plus two S.D. F− = F minus two S.D. N = mean plus two S.D.

seventy-two patients who recovered had peaks of enzyme activity more than twice normal values; only one exceeded 300 units. Curve F of Figure 1 exhibits the mean SGO-T activity of thirty-six patients who died. Curve F+ represents fatalities plus two S.D. and F− represents fatalities minus two S.D. Of ten patients who died on the first day, four had SGO-T activity in the normal range. During the second and third days there were twenty-one deaths with ten of these patients showing a peak level greater than five times the normal. Five patients who died had peak levels exceeding six times normal range.

There was necropsy evidence of acute myocardial infarction in eighteen cases. Seventeen patients had significant elevation of SGO-T activity; the single fatality with normal enzyme activity had a small apical infarction with rupture. On the basis of the material obtained at necropsy, there was acute transmural myocardial infarction with extensive necrosis in those patients who had SGO-T activity greater than five times normal. In two of these patients there was morphologic evidence of extension of the original site of necrosis.

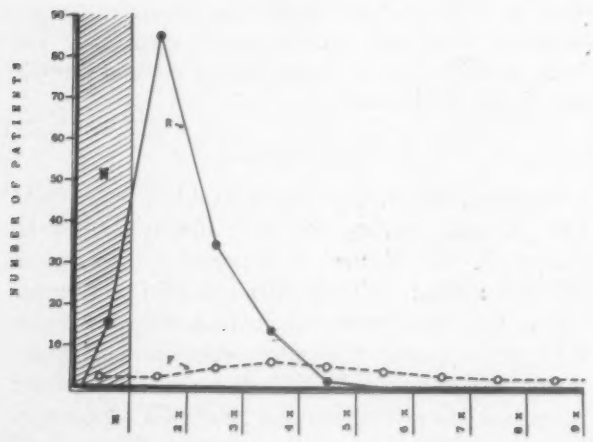


FIG. 2. Relation between mortality and SGO-T activity in multiples of the normal value. N = mean plus two S.D. R = 150 recoveries. F = thirty-six fatalities.

COMMENTS

This study confirms previous observations[1–6] that acute myocardial infarction is characterized by a significant early rise in the SGO-T activity. Only four patients in our group had a normal range of SGO-T activity. These died within three hours after admission. It may be that early death precluded a rise in enzyme activity. The peak of SGO-T was closely related to the immediate prognosis. In those patients who survived after the first day, chances for death exceeded those for recovery at SGO-T readings between four and five times the upper limits of normal (Fig. 2). We agree with the inference of others[1,5,6,9,10] that a poor prognosis accompanies high SGO-T activity. In this study those patients with markedly elevated SGO-T activity had a stormy clinical course with high mortality suggesting that a greatly elevated SGO-T is a sensitive indicator of grave cardiac disease.

Particular reference has been given to one parameter; however, we are aware that prior myocardial infarction, overt clinical shock, ventricular and supraventricular tachycardia and left ventricular failure play significant roles in prognosis. In our group of patients who died,

twelve had overt clinical shock and eighteen had evidence of left ventricular failure. None had right heart failure or clinical evidence of hepatic disease.

From our necropsy and SGO-T data there was no absolute relation between the area of necrosis and the SGO-T activity but the correlation is significant. In general it may be inferred that the greater the enzyme activity the more extensive the area of necrosis and the graver the prognosis.

Summary

This investigation was made on 186 consecutive patients who had serial electrocardiographic changes of acute transmural myocardial infarction. Serum glutamic oxalacetic transaminase activity was measured daily on a colorimeter scale.

An early significant elevation of SGO-T activity was noted in all patients except those who died within three hours after admission. Of those surviving after the first day with enzyme activity less than twice normal values, there were no fatalities.

When the SGO-T activity rose beyond four times the normal range the mortality rate was high. At necropsy those who had normal range of SGO-T activity had small areas of infarction. In contrast, those patients who had four to five times the normal range showed a massive area of myocardial infarction.

Serum glutamic oxalacetic transaminase activity may be a sensitive indicator of grave cardiac disease and is a useful guide in the diagnosis and immediate prognosis of acute transmural myocardial infarction.

Acknowledgment

We wish to express our gratitude to Mr. Edward Rudnick for invaluable assistance during the collection of the data on transaminase.

References

1. LaDue, J. S., Wrøblewski, F. and Karmen, A. The significance of the serum glutamic oxaloacetic transaminase activity following acute myocardial infarction. *Circulation*, 11: 871, 1955.
2. Dewar, H. A., Rowell, N. R. and Smith, A. M. Serum glutamic oxaloacetic transaminase in acute myocardial infarction. *Brit. M. J.*, 5105: 1121, 1958.
3. Murphy, J. G., Sister St. Colum and Magner, J. W. Diagnosis of myocardial infarction. Use of enzyme estimation. *J. Irish M. A.*, 43: 271, 1958.
4. Sampson, J. J. Serum transaminase and other enzymes in acute myocardial infarction. *Prog. Cardiov. Dis.*, 1: 187, 1958.
5. Keele, K. D., Goulden, R. and Newman, M. J. Prognostic and diagnostic value of serum glutamic oxaloacetic transaminase in suspected cardiac infarction. *Lancet*, 2: 1887, 1958.
6. Baron, D. N., Alexander, C. P., Bell, J. L. and Oakley, C. M. Serum transaminase estimation in the investigation of myocardial infarction. *Quart. J. Med.*, 27: 533, 1958.
7. Agress, C. M., Jacobs, H. I., Glassner, H. F., Lederer, M. A., Clark, W. G., Wrøblewski, F., Karmen, A. and LaDue, J. S. Serum transaminase levels in experimental myocardial infarction. *Circulation*, 11: 711, 1955.
8. Reitman, S. and Frankel, S. Colorimetric determination of transaminases. *Am. J. Clin. Path.*, 28: 56, 1957.
9. Bruce, R., Todd, J. D. and LeDune, L. Serum transaminase; its clinical use in diagnosis and prognosis. *Brit. M. J.*, 5105: 1125, 1958.
10. Chinsky, M., Shmagronoff, G. L. and Sherry, S. Serum transaminase activity: observations in a large group of patients. *J. Lab. & Clin Med.*, 47: 108, 1956.

Oral I^{131} Triolein Tolerance Curves in Elderly Subjects with Coronary Artery Disease*

JERRY EDELMAN, M.D., HERSCHEL SANDBERG, M.D., EDWARD R. DICKSTEIN, M.D. *and* SAMUEL BELLET, M.D., F.A.C.C.

Philadelphia, Pennsylvania

I^{131}-LABELED NEUTRAL FATS have been extensively employed to investigate disorders of lipid metabolism since 1949 when Thannhauser and Stanley[1,2] fed olive oil tagged with radioactive iodine to human subjects and observed the rise and fall of the radioactivity in their blood stream. Since that time modifications of this procedure have been used by several investigators[3–7] to study malabsorptive states such as chronic pancreatitis, sprue, carcinoma of the pancreas and the condition following extensive gastric resections. Hyperlipemic states have also been investigated by this technic.[1,8]

Recent studies from this and other laboratories[9,10] have demonstrated that middle-aged subjects with documented evidence of myocardial infarction metabolize orally administered I^{131} triolein in an abnormal manner. Following the ingestion of a labeled fat meal, the radioactivity in the whole blood (WB) and its circulating lipoprotein fraction (TCA) reaches higher levels and remains elevated for at least twenty-four hours compared to those of a control population. In our studies of patients with diabetes mellitus[11] similar abnormalities were found to occur, particularly in subjects with clinically demonstrable atherosclerotic complications. In the diabetic subjects over sixty years of age, however, these elevated blood levels failed to occur. It was, therefore, decided to study oral I^{131} triolein tolerance curves in elderly subjects with coronary artery disease.

MATERIAL AND METHODS

Twenty-six subjects from the medical wards of Philadelphia General Hospital who showed clinical and electrocardiographic evidence of coronary artery disease were utilized in this study. These were divided into two groups. Group A consisted of ten subjects who were sixty years of age or older. Group B consisted of sixteen persons who were less than sixty years of age. A detailed analysis of their age and weight distribution is presented in Table 1. Two days before the administration of the test meal these subjects received twenty drops of Lugol's solution daily. After an overnight fast the test meal described by Beres et al.[3] consisting of I^{131} triolein, ginger ale and milk was administered to these subjects. Oxalated blood samples were then obtained two, four, six, eight and twenty-four hours after administration of the test meal and were analyzed for radioactivity in the whole blood (WB) and trichloracetic acid precipitable fraction (TCA) in a manner previously described.[9] The maximum values of these parameters in each of the subjects were designated WB^p and TCA^p, respectively, and are so tabulated in Table 1. In several instances the serum cholesterol and phospholipids were also determined.

RESULTS

Maximum Activity in the Circulating Blood (WB^p): The mean values of WB^p found in the subjects in Group A (sixty years of age or older) were 11 ± 2 per cent of the ingested radioactivity; the mean values in Group B (less than sixty years of age) were 16.5 ± 3.6 per cent. The individual values are tabulated in Table 1 along with the mean values found in twenty previously reported normal control subjects.

Figure 1 graphically illustrates these results. It is readily observed that the elevated levels found in the subjects under sixty years of age (Group B) are not observed in the older group (Group A).

Maximum Activity in the Circulating Lipoprotein Fraction (TCA): The mean values of the maximum circulating lipoprotein (TCA precipitable fraction of the blood) are shown in Table 1. In

* From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania. This work was aided by a grant from the United States Public Health Service (H4153).

TABLE I

Oral I^{131} Triolein Tolerance Test Values in Twenty-Six Patients with Coronary Artery Disease

Case No.	Age (years)	Weight (pounds)	WB^{p}* (%)	TCA^{p}† (%)	WB^{24}‡ (%)	TCA^{24}§ (%)	Serum Cholesterol Levels (mg. per 100 ml.)
Group A. Patients Sixty Years of Age or Older							
1	65	144	9.8	5.6	7.6	0.76	166
2	70	122	9.8	5.5	5.7	0.35	136
3	70	155	16.1	8.9	5.9	0.68	248
4	64	96	9.8	4.6	5.3	0.88	222
5	78	146	10.3	2.8	3.1	0.16	...
6	68	145	11.2	4.2	4.9	0.31	...
7	60	142	13.0	3.0	3.6	0.36	...
8	60	124	10.7	4.1	7.3	1.3	247
9	64	153	8.6	4.4	...	...	270
10	86	110	11.0	3.8	3.8	0.3	233
Mean	...	...	11.0 ± 2.0	4.7 ± 1.7	5.2 ± 1.5	0.57 ± 0.35	...
Group B. Patients Under Sixty Years of Age							
11	40	202	21.9	13.1	4.3	0.46	145
12	57	163	24.4	7.9	11.5	0.59	160
13	47	163	18.1	12.4	2.8	0.32	242
14	48	142	16.9	7.9	2.7	0.34	243
15	37	156	13.0	6.3	3.3	0.36	168
16	54	160	15.9	5.4	7.1	0.28	...
17	51	141	11.7	8.0	7.7	0.57	...
18	46	195	11.9	3.2	Patient died		
19	57	160	14.1	4.1	5.5	0.47	...
20	35	123	21.5	9.7	5.1	0.70	197
21	57	110	12.6	6.8	2.3	0.23	...
22	58	136	17.0	9.0	4.9	0.63	...
23	58	159	12.6	7.7	7.0	0.81	...
24	48	160	17.7	8.9	3.8	0.50	343
25	48	177	17.1	10.9	6.6	1.70	293
26	44	199	17.5	8.0	4.8	1.4	229
Mean	...	...	16.5 ± 3.6	8.1 ± 2.6	5.3 ± 2.3	0.62 ± 0.41	...
Mean of twenty normal control subjects			11.0 ± 3.5	4.5 ± 1.5	2.9 ± 1.5	0.6 ± 0.37	...

* WB^{p} = Maximum radioactivity values in blood; † TCA^{p} = maximum lipoprotein fraction in blood; ‡ WB^{24} = radioactivity in blood after twenty-four hours; § TCA^{24} = lipoprotein fraction in blood after twenty-four hours.

Group A the mean values of TCA^{p} were 4.7 ± 1.7 per cent. The mean values of Group B were 8.1 ± 2.6 per cent of the ingested radioactivity. These values are graphically illustrated in Figure 2; the elevated levels of the circulating lipoprotein fraction of Group B are not seen in Group A.

The values found in the whole blood and circulating lipoprotein at the end of twenty-four hours show wide variations. There is no statistically significant difference between the two groups.

Typical I^{131} triolein tolerance curves of two patients, one more than sixty years of age and

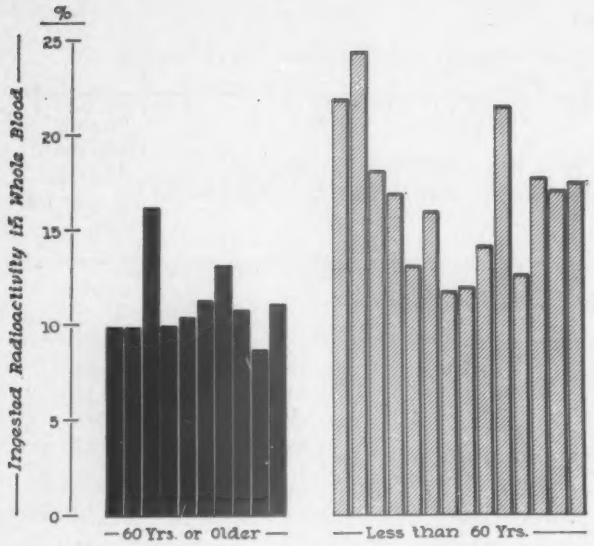


FIG. 1. This illustrates the per cent of ingested radioactivity present in the circulating blood stream of patients with coronary artery disease (estimating the blood volume as 7.7 per cent of the body weight). Each column represents an individual subject. The height of the column represents the per cent of administered radioactivity. The solid columns on the left refer to subjects sixty years of age or older with coronary artery disease (Group A); the hatched columns on the right refer to the subjects less than sixty years of age (Group B). It is readily observed that much higher values are found in the younger population than in those in the sixty years or older group.

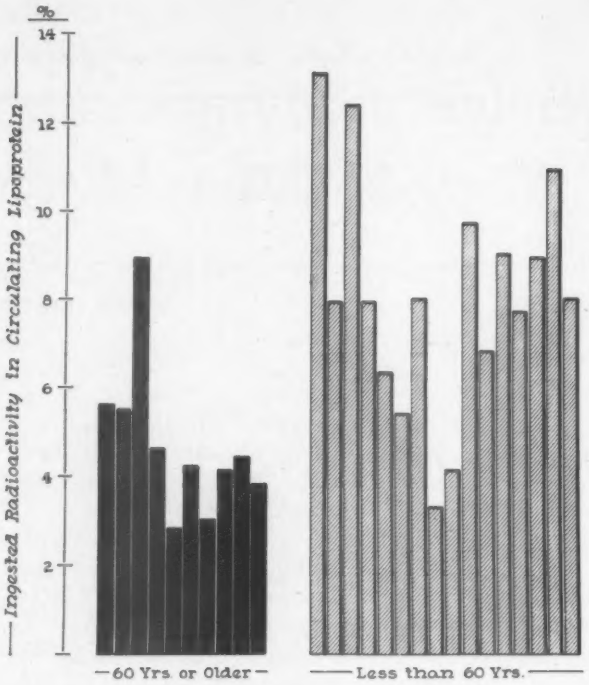


FIG. 2. This illustrates the per cent of ingested radioactivity present in the circulating lipoprotein fraction of patients with coronary artery disease. The solid columns on the left represent subjects sixty years of age or older (Group A); the hatched columns on the right represent subjects less than sixty years of age (Group B). It is clearly observed that much higher values are found in the younger population than those in the sixty years of age or older group.

the other less than sixty years of age, each with coronary artery disease, and of a normal control subject are shown in Figure 3.

COMMENTS

From these data, it is apparent that subjects under sixty years of age with coronary artery disease metabolize I^{131} triolein administered orally in a different manner from the group over sixty years of age. The elevated levels of radioactivity noted in the whole blood and circulating lipoprotein fraction of the younger group fail to appear in the older subjects. These results are similar to those found in our patients with diabetes mellitus who were given oral I^{131} triolein.[11] The younger population again showed elevated levels of radioactivity in these fractions whereas the older subjects failed to do so. Records of the young, normal control subjects previously reported[9] showed values similar to those of the elderly diabetics and patients over sixty years of age with coronary artery disease.

When I^{131} triolein was administered intravenously, both to patients with coronary artery disease and to a control population, no differences could be detected in the rate of disappearance of the radioactivity from the blood stream of the two groups. Moreover, there did not appear to be any relationship between the ages of the subjects and the type of disappearance curves obtained.[12] Increased absorption or deficient utilization of the radioactive lipid could account for the elevated blood levels in the younger group with coronary artery disease, and impairment of this absorption in the older population could prevent the appearance of elevations in the group sixty years of age or older. Further evidence for the latter assumption has been furnished by Necheles and co-workers[13–18] who demonstrated a diminution of intestinal absorption of galactose in older subjects[13] and a significant decrease in pancreatic and blood lipase.[14,15] From their studies with chylomicron curves in elderly subjects and normal control subjects they noted a difference between the two groups which was interpreted as evidence of delayed absorption in aged persons.[16–18] It is also interesting to

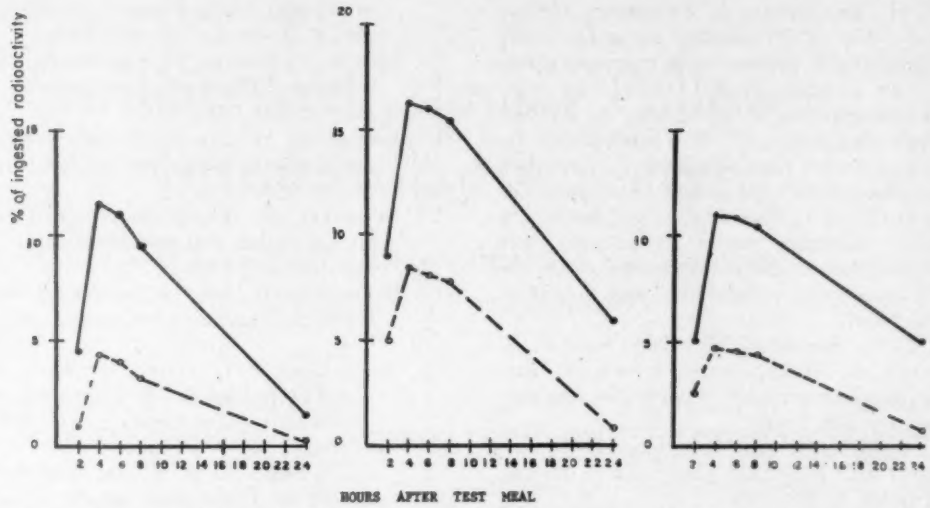


FIG. 3. Shown are the typical I^{131} triolein tolerance curves in a normal control subject (left), a patient less than sixty years of age with coronary artery disease (Case 22) (middle), and one more than sixty years of age with coronary artery disease (Case 6) (right). The abscissa represents time in hours after ingestion of the fat meal. The ordinate represents the per cent of ingested radioactivity appearing in the whole blood (solid upper line) and in the circulating lipoprotein fraction (broken lower line). (The blood volume was estimated as 7.7 per cent of the body weight.)

note that Ackermann,[19] in a recent study of blood lipids in relation to the process of aging, found that serum cholesterol increases with age up to fifty years in men and sixty in women and then decreases with further increase in age to values close to those of younger persons. There was a somewhat similar change in the total fatty acids and a less marked change in the polyunsaturated fatty acids. Mattingly,[20] however, in his recent comprehensive study has shown that a significant increase occurs in the mean cholesterol values in normal subjects aged thirty-five to forty-four as compared to those aged twenty-five to thirty-four, but no significant increase was seen in those aged forty-five to fifty-nine as compared to the group from thirty-five to forty-four years of age.

SUMMARY

1. Oral I^{131} triolein tolerance curves were performed on ten subjects with coronary artery disease, sixty years of age or older, and on sixteen subjects who were less than sixty years old.

2. Elevated levels of radioactivity were found in the whole blood and circulating lipoprotein fraction of the younger group.

3. Values similar to those in normal control subjects were found in the older subjects.

4. The results were attributed to a difference in lipid absorption between the older and younger groups.

ACKNOWLEDGMENT

Mrs. Ulana Soss and Lois Gelber offered valuable technical assistance in this study.

REFERENCES

1. THANNHAUSER, S. J. and STANLEY, M. M. Serum fat curves following oral administration of I^{131} labelled neutral fat to normal subjects and those with idiopathic hyperlipemia. *Tr. A. Am. Physicians*, 62: 245, 1949.
2. STANLEY, M. M. and THANNHAUSER, S. J. The absorption and disposition of orally administered I^{131} labelled neutral fat in man. *J. Lab. & Clin. Med.*, 34: 1634, 1949.
3. BERES, P., WENGER, J. and KIRSNER, J. B. The use of I^{131} triolein in the study of absorptive disorders in man. *Gastroenterology*, 32: 1, 1957.
4. RUFFIN, J. M., SHINGLETON, W. W., BAYLIN, G. J., HYMANS, J. C., ISLEY, J. K., SAUNDERS, A. R. and SOHMER, M. F. I^{131} labelled fat in the study of intestinal absorption. *New England J. Med.*, 255: 594, 1956.
5. BERKOWITZ, D. and SKLAROFF, D. The use of radioactive fat in the study of absorption in various disease states. *Arch. Int. Med.*, 100: 951, 1957.
6. TURNER, D. A. The absorption, transport and deposition of fat; application of a new method for the determination of I^{131} lipid activity in dogs and man. Part I and Part 2. *Am. J. Digest. Dis.*, 13: 594, 1958.
7. DUFFY, B. J., JR. and TURNER, D. A. The differential diagnosis of intestinal malabsorption with I^{131} fat and fatty acid. *Ann. Int. Med.*, 48: 1, 1958.
8. KRUGER, F. A., CORNWELL, D. G., HAMWI, G. J. and BROWN, J. B. Investigation of serum lipoprotein metabolism in man with I^{131} labeled triolein. *Am. J. Clin. Nutrition*, 8: 44, 1960.

9. Seller, R. H., Brachfeld, J., Sandberg, H. and Bellet, S. Use of I^{131} labelled fat in the study of lipid handling in patients with coronary artery disease. *Am. J. Med.*, 27: 231, 1959.
10. Likoff, W., Berkowitz, D., Woldow, A., Jacobs, A. G. and Sklaroff, D. N. Radioactive fat absorption patterns; their significance in coronary artery atherosclerosis. *Circulation*, 18: 1118, 1958.
11. Sandberg, H., Min, B., Feinberg, L. and Bellet, S. I^{131} triolein tolerance curves in patients with diabetes mellitus: their similarity to those observed in myocardial infarction. *Arch. Int. Med.*, 105: 866, 1960.
12. Feinberg, L. J., Sandberg, H., Dickstein, E. R. and Bellet, S. Disappearance curves of intravenously administered I^{131} triolein in humans. *Fed. Proc.*, 19: 228, 1960.
13. Meyer, J., Sorter, H. and Necheles, H. Studies in old age. VII. Intestinal absorption in old age. *Gastroenterology*, 1: 876, 1943.
14. Necheles, H., Plotke, F. and Meyer, J. Studies in old age: Active pancreatic secretion in aged. *Am. J. Digest. Dis.*, 9: 157, 1942.
15. Meyer, J., Sorter, H. and Necheles, H. Studies in old age: Blood enzymes in aged. *Am. J. Digest. Dis.*, 9: 160, 1942.
16. Becker, G. H., Meyer, J. and Necheles, H. Fat absorption in young and old age. *Gastroenterology*, 14: 80, 1950.
17. Necheles, H. The phenomenon of chylomicrons in fat absorption and arteriosclerosis. *Am. J. Digest. Dis.*, 18: 229, 1951.
18. Becker, G. H., Meyer, J. and Necheles, H. Fat absorption and atherosclerosis. *Science*, 110: 529, 1949.
19. Ackermann, P. G., Toro, G., Toro, J., Kheim, T. and Kountz, W. B. Blood lipids in young and old individuals. *Clin. Chem.*, 5: 100, 1959.
20. Mattingly, T. W., Parmley, L. F., Jr., Durrum, E. L., Smith, E. R. B. and Hyatt, M. R. Lipid studies in health and disease *J.A.M.A.*, 170: 536, 1959.

Cardiac Arrhythmias Following Intracardiac Surgery*

MICHAEL D. RABBINO, LEONARD S. DREIFUS, M.D. *and* WILLIAM LIKOFF, M.D., F.A.C.C.
Philadelphia, Pennsylvania

SURGICAL procedures for the correction of acquired and congenital heart disease have frequently been associated with disturbances of impulse formation and conduction. A multiplicity of factors including surgical trauma to certain sensitive areas of the myocardium, hypothermia, hypoxia, excessive or insufficient digitalis administration and electrolyte imbalance has contributed to the development of cardiac arrhythmias during or following surgery.

Rogers, Wroblewski and LaDue[1] noted that operations in the thorax were found to be most frequently accompanied by cardiac arrhythmias. MacCuish[2] and Burback et al.[3] have brought attention to the frequent occurrence of auricular arrhythmias (particularly auricular fibrillation) following mitral commissurotomy. Sasaki et al.[4] noted a significant relationship between the development of supraventricular arrhythmias and the surgical repair of atrial and ventricular septal defects under hypothermia.

It is the purpose of this study to determine the relative incidence of the major arrhythmias associated with cardiac surgery. Through an analysis of these cases it is hoped that a rational approach to the management of patients undergoing operative correction for cardiac defects may be established with specific reference to the prevention and treatment of arrhythmias.

METHODS AND MATERIALS

All records of the 211 patients undergoing cardiac surgery during the period of January 1959 through November 1959 at the Hahnemann Medical College and Hospital were selected for review. This study included all patients having serious cardiac arrhythmias following operative intervention. Excluded were patients having occasional auricular or ventricular premature beats, sinus tachycardia and intraventricular conduction defects.

This review did not consider those patients who died during the surgical procedure or who died suddenly following operation due to cardiac arrest with or without antecedent ventricular fibrillation. In this latter group, electrocardiograms were usually not available, and clinically the cases did not represent a problem of postoperative medical management. There were 157 patients (74 per cent) operated on under direct vision with the aid of total bypass and hypothermia. The other fifty-four patients (26 per cent) underwent closed procedures (Table I).

RESULTS

Of the 211 patients undergoing cardiac surgery during this period, 152 had rheumatic, forty-nine congenital, eight atherosclerotic and one idiopathic heart disease (Table II). Serious arrhythmias developed in the postoperative period in thirty-nine patients (18.5 per cent).

The most frequent disturbance of rhythm following cardiac surgery was atrial fibrillation (Fig. 1) which developed in ten patients (Table III). Other rapid atrial rhythms were seen less frequently, atrial flutter occurring in four and atrial tachycardia in two.

Nonparoxysmal nodal tachycardia†[5] was quite frequent (Figs. 2, 3) and was associated with incomplete A-V dissociation in nine (Fig. 2), reciprocal rhythm in two, and complete A-V dissociation‡ in two. Ventricular bigeminy

† Nonparoxysmal nodal tachycardia represents enhanced nodal activity (rate 70 to 130) without the sudden onset or termination of the mechanism which is characteristic of the paroxysmal forms.

‡ A-V dissociation indicates independence of pacemaker control of the atria and ventricles. This may be due to: (1) interference of the pacemakers controlling the atria and ventricles, (2) high grade A-V heart block, or (3) a combination of the two factors. If impulses are permitted to be conducted forward or retrograde through the A-V junction, the dissociation is "incomplete." These beats are termed "captures" since either the atria or ventricles are "captured" by the other pacemaker. On the other hand, complete A-V dissociation is present when absolutely no impulses of either pacemaker are permitted to pass the A-V junction.

* From the Department of Medicine, Section of Cardiovascular Diseases, Hahnemann Medical College, Philadelphia, Pennsylvania.

TABLE I

Correlation of the Type of Heart Disease, Operative Procedure and Incidence of Cardiac Arrhythmias

Type of Heart Disease	Anatomic Diagnosis	Procedure	Surgical Approach	Total No. of Cases	No. of Arrhythmias
Rheumatic	Mitral stenosis	Mitral commissurotomy	C*	35	7 (20%)
	Mitral stenosis	Mitral commissurotomy	O-H†	15	3 (20%)
	Mitral insufficiency	Mitral plication	O-H	31	10 (32%)
	Aortic stenosis	Aortic commissurotomy	O-H	36‡	4 (11%)
	Aortic insufficiency	Aortic bicuspidation	O-H	23	4 (17%)
	Combined mitral and aortic valvular disease	Combined mitral and aortic valvuloplasty	O-H	12	3 (25%)
Congenital	Atrial septal defect	Atrioseptopexy	C	10	2 (20%)
	Atrial septal defect	Atrioseptopexy	O-H	5	2 (40%)
	Ventricular septal defect	Ventriculoseptopexy	O-H	10	0
	Tetralogy of Fallot	Pulmonic resection and ventriculoseptopexy	O-H	9	3 (33%)
	Tetralogy of Fallot	Blalock anastomosis	C	2	0
	Patent ductus arteriosus	Ligation and excision	C	6	0
	Pure pulmonic stenosis	Resection of pulmonic valve	O-H	1	0
	Coarctation of aorta	Resection	C	5	0
	Transposition	Correction	O	1	0
Atherosclerotic	Coronary sclerosis	Endarterectomy	O-H	5	1 (20%)
	Coronary sclerosis	Poudrage	C	1	0
	Coronary sclerosis	Mammary artery implantation	C	1	0
	Ventricular aneurysm	Excision	O-H	1	0
	Aortic aneurysm	Excision	O-H	1	0
Other (idiopathic)	Constrictive pericarditis	Pericardiectomy	C	1	0

* C = closed. † O-H = open with hypothermia. ‡ One case performed closed.

occurred in three patients with nodal mechanisms (Fig. 4), two of whom had complete and one incomplete A-V dissociation. Persistent ventricular bigeminy was seen in six instances and idioventricular rhythm in one other case.

In the sixteen patients incurring disturbances of atrial rhythm, twelve reverted to regular sinus rhythm, one to the preoperative nodal mechanism and three persisted in atrial fibrillation (Table IV). Frequently, discontinuance of digitalis with the development of a nodal rhythm engendered rapid atrial mechanisms (Fig. 5).

Nonparoxysmal nodal rhythms with incomplete A-V dissociation were usually transient, ten of thirteen patients spontaneously reverting to their preoperative rhythm within twenty-four hours. However, two patients with tetralogy of Fallot died with this mechanism. Three patients with nodal rhythm complicated by ventricular bigeminy (two of whom were operated on in the presence of digitalis overdosage) returned to their preoperative rhythm following therapy (Fig. 4).

Of the seven patients whose postoperative course was complicated by ventricular ectopic rhythms, three died. In one patient death could be attributed to a cerebral vascular oc-

TABLE II

Incidence of Postoperative Arrhythmias in the Various Types of Heart Disease

	Total No. of Cases	Patients Having Serious Postoperative Arrhythmias	
		No.	Percentage
RHD*	152	31	20.4
CHD†	49	7	14.3
ASHD‡	8	1	12.5
Other§	1	0	0.0
Total	211	39	18.5

* Rheumatic heart disease.
† Congenital heart disease.
‡ Atherosclerotic heart disease.
§ Idiopathic heart disease.

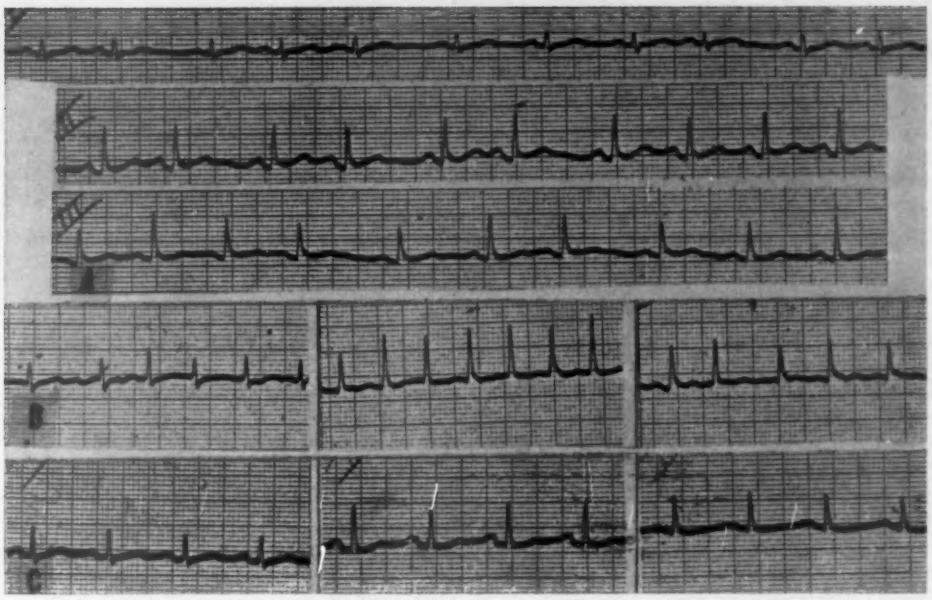


FIG. 1. A, preoperative record (October 13) taken ten days prior to mitral commissurotomy. Leads I, II and III are shown. While the patient was maintained on digitalis medication, frequent premature atrial beats were present. B, following surgery (October 23). Atrial fibrillation with a rapid ventricular response has developed. C, October 26. Conversion to normal sinus rhythm following intravenous Cedilanid medication. The presence of premature atrial systoles in the preoperative electrocardiogram was a premonitory sign of a more serious rapid supraventricular arrhythmia developing during or immediately following the intracardiac procedure.

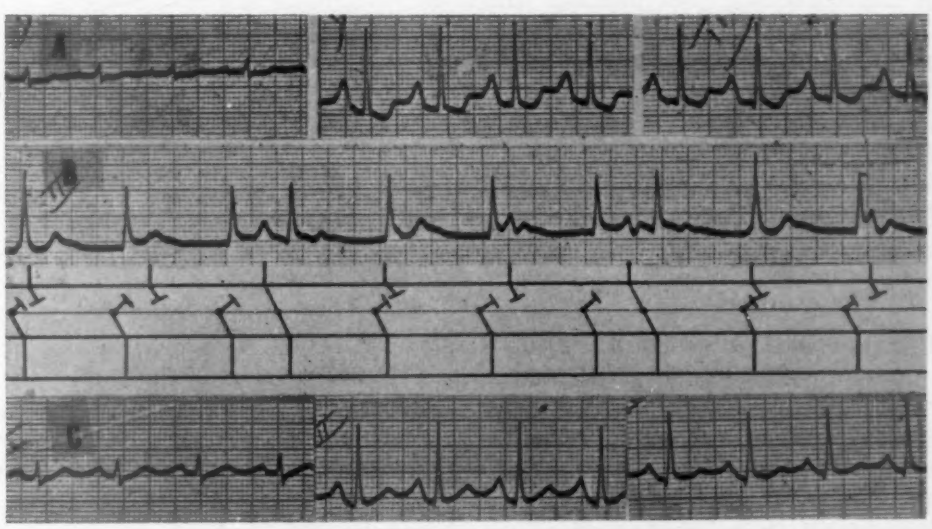


FIG. 2. A, preoperative curve (July 7, leads I, II and III) demonstrates an abnormal P wave with prolonged P-R interval as well as digitalis effects. B, following mitral commissurotomy (July 17, lead II) an irregular rhythm is noted with periods of bigeminy. The atria are under the control of the sinus node at 60/minute. However, a nonparoxysmal nodal rhythm at 75/minute interrupted by "premature beats" controls the ventricles. These early beats are actually ventricular captures and the tracing constitutes an incomplete A-V dissociation due to interference. (See diagrammatic tracing.) Hence, patency of the A-V junction is confirmed. The ST-T alterations may be ascribed to the postoperative pericarditis as well as digitalis effects.[8] C, tracing one week later (July 24, leads I, II and III). Sinus rhythm was re-established spontaneously, with digitalis being maintained throughout this period.

TABLE III
Classification of Major Postoperative Arrhythmias

Type of Arrhythmia	No. of Cases
Atrial	
Tachycardia	2
Flutter	4
Fibrillation	10
Nodal	
Nonparoxysmal tachycardia with incomplete A-V dissociation	9
Nonparoxysmal tachycardia with complete A-V dissociation	2
Nonparoxysmal tachycardia with reciprocal rhythm and 2° retrograde block	2
Nodal with ventricular bigeminy	
Nonparoxysmal tachycardia with incomplete A-V dissociation plus ventricular bigeminy	1
Nonparoxysmal tachycardia with complete A-V dissociation and ventricular bigeminy	2
Ventricular	
Ventricular bigeminy with or without multifocal premature systoles	6
Idioventricular rhythm	1
Total	39

TABLE IV
Results of Therapy

Type of Postoperative Arrhythmia	Returned to Preoperative Rhythm	Discharged with Arrhythmia	Died
Atrial	13	3	0
Nodal*	10†	1	2‡
Ventricular premature systoles causing ventricular bigeminy	4	0	3§
Mixed: Nodal tachycardia (with ventricular premature systoles)	3	0	0

* Three patients developed complete right bundle branch block secondary to surgery (two died subsequently).

† Two patients developed atrial flutter before reverting to normal sinus rhythm (due to withdrawal of digitalis).

‡ Both patients had tetralogy of Fallot.

§ One patient died, probably secondary to cerebral embolism; one patient went to surgery with digitalis excess.

TABLE V
Precipitating Causes of Postoperative Cardiac Arrhythmias

Type of Arrhythmia	Surgery	Under digitalization	Over-digitalization	Surgery Overdigitalization
Atrial	6	10	...	...
Nodal	12	...	...	1
Ventricular	3	...	3	1
Mixed: Nodal tachycardia with ventricular premature systoles	1	...	2	1

clusion. Of the remaining two patients who died, one had tetralogy of Fallot and the other had been operated on in the presence of digitalis toxicity.

Open heart procedures were more frequently associated with serious arrhythmias (Table I). There was no apparent difference in the incidence of arrhythmias following mitral as opposed to aortic valvular surgery.

COMMENTS

It should be stated that although this study is concerned with the evaluation of "postoperative" arrhythmias, it is realized that many of the arrhythmias were actually induced during the surgical procedure. There are several obvious shortcomings inherent in this type of review which should be acknowledged at the onset. Firstly, only those patients who had arrhythmias that were clinically recognized had postoperative electrocardiograms taken. Hence, transient arrhythmias or others that may have gone undetected were not included. One additional criticism should be raised, namely, that the operative mortality for the different cardiac lesions varied greatly. It is a truism that a given patient must survive the surgery if a postoperative arrhythmia is to develop. Therefore, those patients undergoing "high risk" surgery (e.g., aortic valvular diseas ventricular septal defect with or without pul monic stenosis and transposition of the grea vessels) would tend to have an artificially lowered incidence of arrhythmias. Those undergoing "low risk" surgery (e.g., closed mitral commissurotomy) would tend to have an artificially elevated incidence.

Precipitating Factors: The above should not detract from what can be learned from this study, for the incidence and types of arrhythmias reported still represent the results in a large series of operated cases. And furthermore,

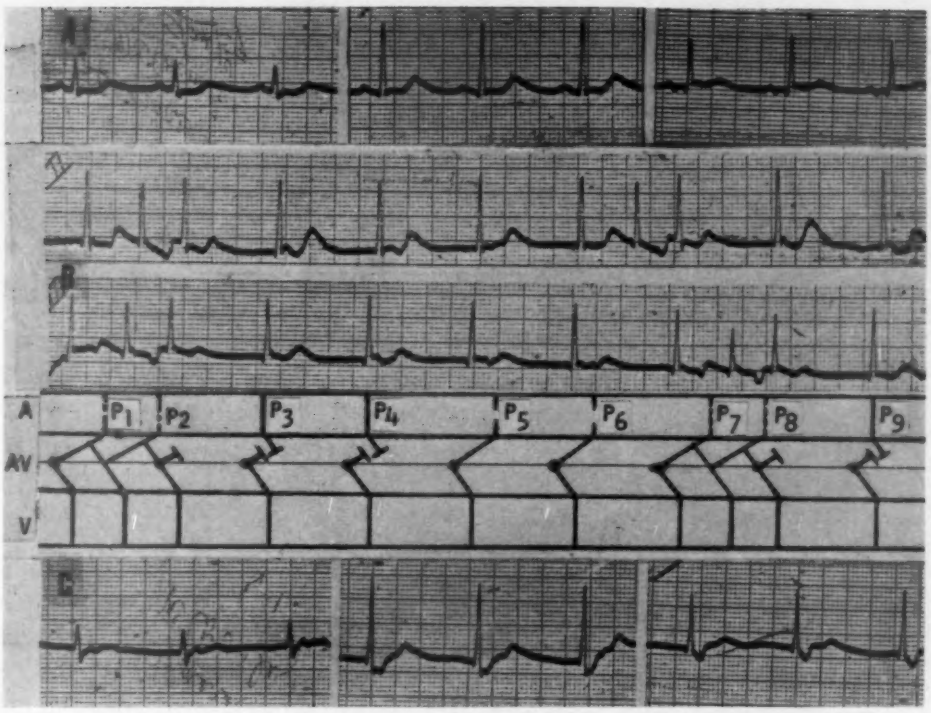


FIG. 3. A, preoperative curve (May 2, leads I, II and III) shows a regular sinus rhythm. B, following mitral and aortic commissurotomy (May 21, leads II and III), an unusual arrhythmia causing group beating (trigeminy) is illustrated. A nonparoxysmal A-V nodal tachycardia is present with progressively lengthening retrograde conduction. (See diagram below lead III) There is a competition between these retrograde nodal impulses (rate 71) and somewhat slower ones (rate 67) originating in the sinus node. At P_3 and P_4 the sinus impulses are in complete control of the atria and interfere with the nodal impulse in the A-V junction, resulting in A-V dissociation. Then at P_5 and P_6, the point of interference shifts to the atria resulting in atrial fusion beats. Eventually, at P_6 and P_8 the tachycardia includes the sinus node. Coincidentally, however, as the R-P interval lengthens, repetitive re-entry ensues in the A-V junction which results in two reciprocal beats. Continuation of the re-entry process is prevented by block of the retrograde impulses which permits "escape" of the sinus node (P_9) and classic resumption of dissociation. "Atrial captures" in this instance establish patency of the A-V junction. C, tracing on June 1, leads I, II and III, after digitalis was discontinued. Accelerated nodal activity persists at a slightly lower rate (68), but the retrograde conduction is shorter and remains constant. The patient was discharged with a nodal rhythm.

they may serve as a basis of comparison with similar groups. From the analysis of the arrhythmia, its date of onset, duration, and the results of therapy, it was possible to postulate the primary factor involved in the production of the specific arrhythmia in each patient (Table v). All rapid atrial arrhythmias were either surgically induced (six patients) or secondary to preoperative inadequate digitalization (ten patients) (Table v, Fig. 1). Nodal rhythms without ventricular beats were almost exclusively due to surgery (twelve of thirteen patients) (Figs. 2 and 3). Ventricular arrhythmias were secondary to surgery (three patients), overdigitalization (three patients) or a combination of the two (one patient). Of those developing nodal rhythms with ventricular beats (three patients) (Fig. 4), two could be ascribed to digitalis toxicity as well as surgical trauma and one to the effects of surgery alone.

Although it may be a moot point, it should be added that regardless of the nature of the arrhythmia which developed, surgery was the factor which precipitated its development. In those cases in which surgical trauma itself did not directly induce disturbances in impulse formation and conduction, it seems likely that surgery was the stressful situation which accentuated the basic underlying problem, whether it was the adequacy of digitalization or the extent of intrinsic myocardial disease.[6]

As shown in Table I, open procedures (carried out with the aid of hypothermia) were more frequently associated with serious arrhythmias.

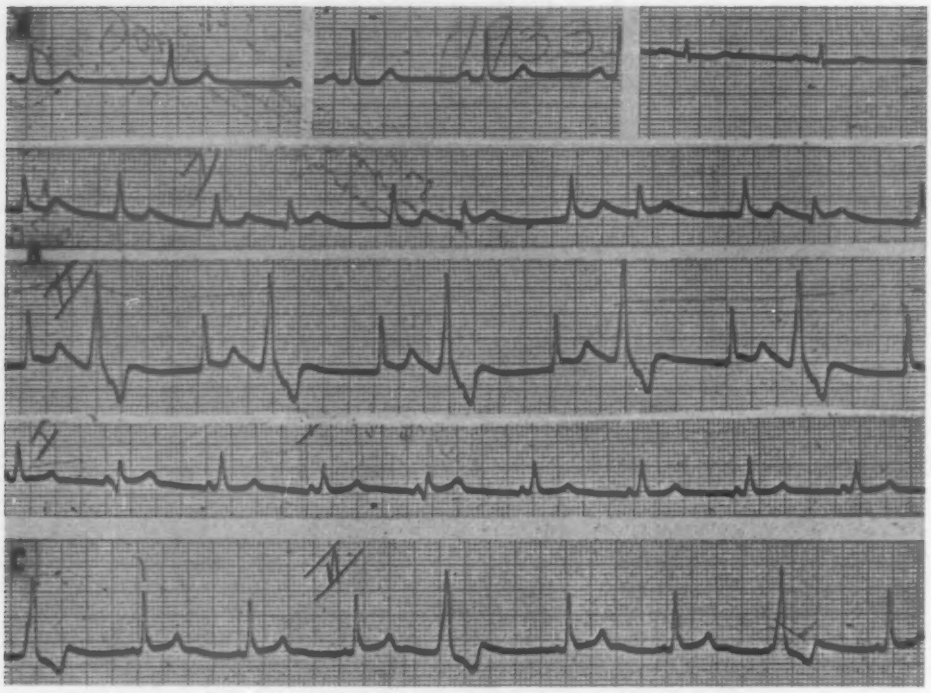


FIG. 4. A, regular sinus rhythm is seen (February 25, leads I, II and III). On February 27, one day prior to mitral commissurotomy, a large supplemental dose of digitalis (0.5 gm.) was administered to the patient. B, on February 28, a nodal rhythm with coupled ventricular premature systoles was recorded (leads I and II). The notching on the S-T segment of the ventricular premature systoles represents a retrograde P wave. This would also suggest that the nodal beats may have retrograde conduction and exclude A-V block. The ST-T alterations represent the combination of pericarditis plus digitalis effects.[8] C, tracing on March 2 (leads I and II). The P-R interval is 0.09 second. The P waves are upright and are of a different contour than in A. The appearance of this rhythm under these circumstances would suggest that the pacemaker actually arises close to the tail of the A-V node (coronary nodal rhythm). The ventricular premature beats observed in B were attributed to digitalis excess. Following potassium chloride and procaine amide therapy, a coronary nodal rhythm was established with less frequent ventricular premature systoles.

This is in keeping with the findings of Sasaki et al.[4] Several years ago, Jaruszewski, Hellerstein and Feil[7] first called attention to a high incidence of cardiac arrhythmias in cyanotic patients undergoing cardiac surgery. Undoubtedly, the duration of the surgical procedure and the degree of body cooling were primary factors.

Although multiple electrocardiograms were taken in the preoperative period, it became apparent that tracings taken immediately prior to surgery contained important clues to the likelihood of the precipitation of a serious arrhythmia. In the vast majority of cases in which rapid atrial rhythms developed, atrial premature systoles were seen in the preoperative electrocardiogram (Fig. 1). Furthermore, more serious manifestations of these problems developed invariably in patients demonstrating evidence of digitalis excess or insufficient digitalis therapy.

Treatment: In this series of cases, rapid atrial arrhythmias, which occurred most frequently on the third postoperative day, but also as late as seven to fourteen days following surgery, were invariably treated with digitalis. When conversion was unsuccessful, quinidine was usually tried in addition. Nodal rhythms were almost invariably secondary to surgical trauma. The benign nature of these latter nodal mechanisms with incomplete A-V dissociation is evidenced by the fact that they appeared immediately after surgery and lasted less than twenty-four hours in most cases regardless of therapy. The presence of "capture beats" indicated patency of the A-V junction (Figs. 2 and 3). On the other hand, A-V dissociation due to complete A-V heart block (Fig. 6) (usually engendered by the placement of a suture in or near the A-V junction) was a sinister sign unless immediately relieved. An internal pace-

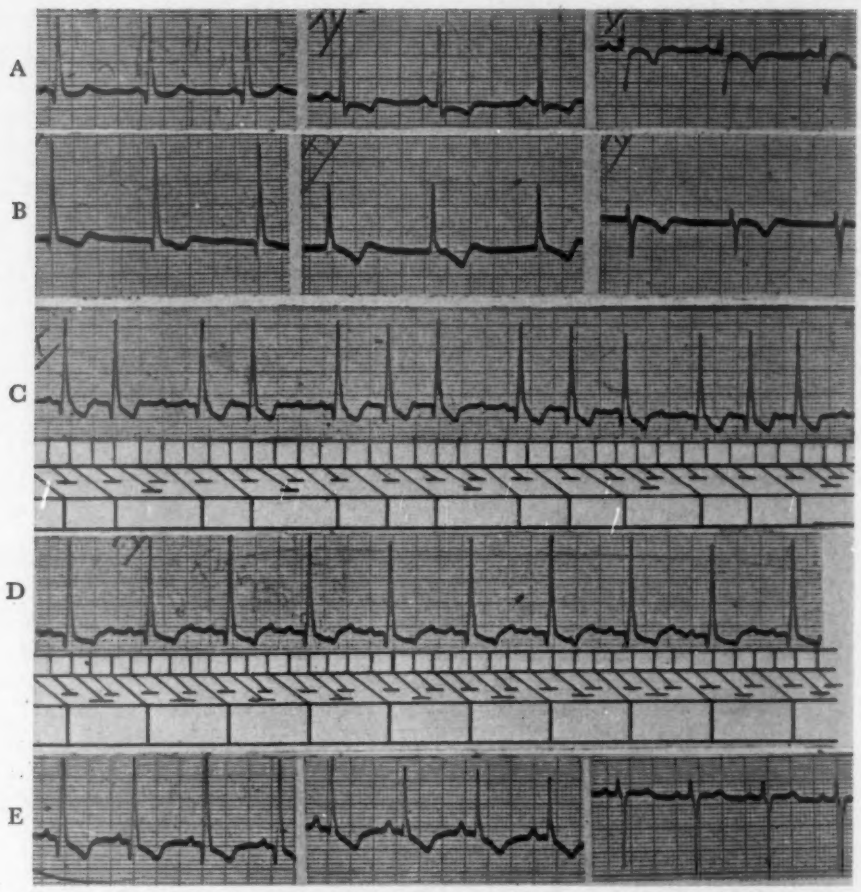


FIG. 5. A, taken prior to operation (January 19, leads I, II and III) illustrates a sinus rhythm in the presence of left ventricular hypertrophy and digitalis effects. B, January 23. Following aortic bicuspidization for rheumatic aortic insufficiency, a nonparoxysmal nodal tachycardia at 68/minute was recorded. No P waves are seen and atrial fibrillation may be present. Digitalis medication was discontinued and on January 28 a rapid irregular rhythm was noted. C, January 28, lead I. An auricular flutter at 300/minute is present with group ventricular beating (bigeminy as well as trigeminy). As can be seen in the diagram, every other atrial impulse is blocked high up in the A-V junction due to physiologic interference caused by the normal refractoriness in the face of rapid stimulation of the A-V junction.[9] There is a progressive prolongation of the P-R interval of the conducted beats until the P-R interval becomes infinite, the impulse being blocked in the lower regions of the A-V junction due to second degree A-V block of the Wenckebach type. A "pseudobigeminy" results from a 2:1 conduction ratio in the upper regions of the A-V junction, and a 3:2 conduction ratio in the lower regions.[9] Furthermore, a "pseudotrigeminy" is engendered by persistent physiologic 2:1 conduction in the upper regions of the A-V junction, and 4:3 conduction ratios in the lower regions. D, January 29, lead I. Following redigitalization, the ventricular response was slowed to 88/minute with the establishment of a persistent 2:1 block in the lower regions of the A-V junction, resulting in a 4:1 A-V conduction ratio. E, a sinus rhythm was reestablished on February 3, with the patient on maintenance digitalis therapy. The withholding of digitalis in the presence of a nodal mechanism following cardiac surgery often resulted in rapid atrial rhythms. In this case, a rapid flutter developed with periods of "pseudobigeminy" and "pseudotrigeminy" which at the bedside suggested further evidence of digitalis toxicity. Only careful analysis of the electrocardiogram prompted rapid redigitalization to control the mechanism.

maker with an electrode inserted directly in the myocardium should be left in place prior to closure of the chest. Cardiac arrest in the postoperative period was frequent in this group because of the instability of the subsidary nodal or ventricular pacemakers. Five patients died with these mechanisms. Multifocal ventricular ectopic beats in association with sinus rhythm,

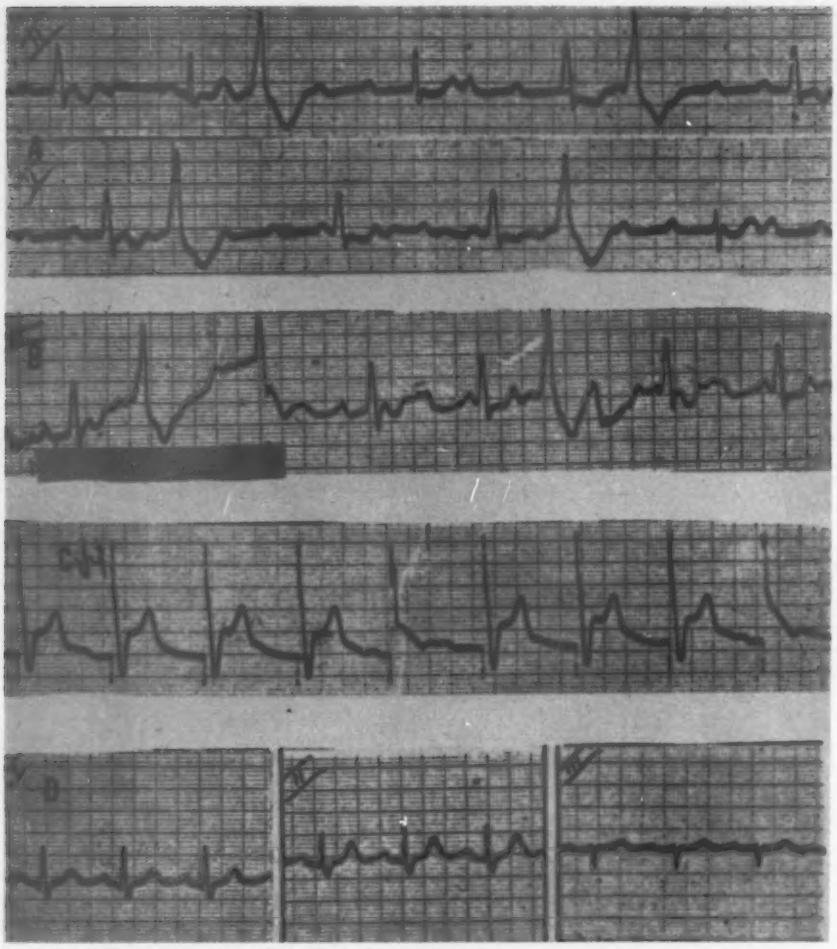


FIG. 6. A, continuous lead II. Sinus tachycardia is present at 130/minute. However, the ventricles are controlled by a nodal pacemaker at 45/minute with frequent ventricular premature systoles. The P waves are not "fixed" in the ventricular cycle and "capture beats" are absent. Hence, complete A-V dissociation due to third degree A-V heart block is present. This was engendered by a suture transfixed near the A-V junction during plication of the mitral valve. Removal of the suture did not immediately allow conduction through the A-V junction. B, isoproterenol sublingually temporarily enhanced A-V nodal impulse formation but the patient remained in severe congestive failure due to the bradycardia. C, utilization of an electrical internal pacemaker controlled the ventricles at 73/minute. D, one week later, sinus rhythm was reestablished and the pacemaker was removed.

atrial fibrillation or nonparoxysmal nodal tachycardia developed immediately following operation, and were secondary to overdigitalization, surgical trauma or both. Digitalis was withheld and potassium administered in all instances. In most cases the effects of digitalis excess were corrected by potassium administration.

Pick and Dominguez[5] described three principal conditions having a common nodal disturbance and leading to either impairment of A-V conduction or to the acceleration of nodal impulse formation or to the combination of the two: (1) digitalis, (2) acute rheumatic fever and (3) recent posterior wall infarction. A fourth condition as seen in association with operative procedures close to the conduction system should be added. The nodal mechanisms seen in our postoperative arrhythmias demonstrated abnormalities in impulse formation as well as conduction. Furthermore, reversion to a sinus mechanism was usually spontaneous within a few days following operation and did not require antiarrhythmic therapy. It was thought that the cause of the nodal tachycardia was surgical trauma in and around the A-V node. In one instance the patient was discharged with a persistent nodal mechanism with a well controlled ventricular response (Fig. 3). On the other

hand, discontinuance of digitalis medication with the appearance of a nodal mechanism resulted in rapid atrial rhythms (Fig. 5). Digitalis should not be withdrawn in these cases and may be further administered if clinically indicated.

Summary

1. Of 211 patients undergoing cardiac surgery, serious postoperative arrhythmias developed in thirty-nine (19 per cent). Atrial fibrillation developed in ten patients, atrial flutter in four and atrial tachycardia in two. Nonparoxysmal nodal tachycardia with incomplete A-V dissociation was seen in nine, with reciprocal rhythm in two and with complete A-V dissociation in two. Ventricular bigeminy occurred in three patients with nodal rhythm, and a persistent ventricular bigeminy in six other patients.

2. Invariably, rapid atrial mechanisms developed in the postoperative period in patients who demonstrated premature atrial systoles in the preoperative period.

3. Electrocardiograms taken immediately prior to surgery frequently suggested important clues to the likelihood of serious postoperative arrhythmias.

4. Open procedures carried out with the aid of hypothermia were more frequently associated with serious arrhythmias.

5. All patients having rapid atrial mechanisms responded to redigitalization. However, if digitalis medication was withheld because of the appearance of nonparoxysmal nodal tachycardia, rapid atrial mechanism frequently resulted.

6. Invariably more serious manifestations of these problems developed in patients exhibiting evidence of digitalis excess or insufficient digitalis therapy.

7. The development of nonparoxysmal nodal tachycardia with incomplete or complete dissociation was usually transient and did not require therapy. Digitalis medication should not be withheld in the presence of this mechanism.

8. The development of persistent ventricular ectopic beating or complete A-V heart block associated with nonparoxysmal nodal tachycardia or ventricular tachycardia was a sinister sign; five patients died with these mechanisms. An internal pacemaker with an electrode directly inserted in the myocardium prior to closure of the chest is indicated in these cases.

9. A fourth cause of nonparoxysmal nodal tachycardia, namely, operative procedures performed close to the conduction system, is described.

Acknowledgment

We are indebted to Dr. Alfred Pick for his valuable criticisms and opinions in the interpretation of the electrocardiograms.

References

1. Rogers, W., Wroblewski, F. and LaDue, J. S. Supraventricular tachycardia complicating surgical procedures. *Circulation*, 12: 192, 1953.
2. MacCuish, R. K. Cardiac arrhythmias following mitral valvulotomy. *Acta med. scandinav.*, 160: 125, 1958.
3. Burback, B., Schwedel, J. B. and Young, D. The role of digitalis in mitral valvuloplasty. *Am. Heart J.*, 54: 863, 1957.
4. Sasaki, R., Theilen, E. O., January, L. E. and Ehrenhaft, J. L. Cardiac arrhythmias associated with the repair of atrial and ventricular septal defects. *Circulation*, 18: 909, 1958.
5. Pick, A. and Dominguez, P. Nonparoxysmal A-V nodal tachycardia. *Circulation*, 16: 1022, 1957.
6. Likoff, W. The treatment of arrhythmias during cardiac surgery. Presented at the American College of Physicians Meeting on Cardiac Arrhythmias, Philadelphia, May 1959.
7. Jaruszewski, E. J., Hellerstein, H. R. and Feil, H. Electrocardiographic studies during cardiac surgery. *Circulation*, 7: 175, 1953.
8. Cahue, A. and Pick, A. Acute alterations of the electrocardiogram following thoracic surgery. *Dis. Chest*, 31: 14, 1957.
9. Besoain-Santander, M., Pick, A. and Langendorf, R. Conduction in auricular flutter. *Circulation*. 2: 604, 1950.

Experimental Studies

The Effect of Experimental Hypothyroidism on Coronary Blood Flow and Hemodynamic Factors*

JOHN C. SCOTT, PH.D., THEODORE A. BALOURDAS, M.D. *and* MILLARD N. CROLL, M.D.
Philadelphia, Pennsylvania

THE EFFECTS UPON cardiodynamics of hyper- and hypothyroidism, particularly the former, have been studied by many investigators.[1] Hypothyroidism in man has been shown to be associated with a reduction in heart rate, cardiac output and arterial pressure.[2] *In vitro* studies of experimentally induced hypothyroidism have demonstrated a reduction in oxygen consumption of the myocardium. However, few reports have appeared describing the relationship between myocardial consumption of oxygen, coronary blood flow and cardiac efficiency in the animals with experimentally produced hypothyroidism. A somewhat comparable situation of hypothermia has been studied in detail.[3]

Since controlled inactivation of the thyroid has been used in recent years as a therapeutic tool in the treatment of angina, more information concerning the effects on myocardial metabolism would seem desirable. The present report deals with results obtained in the dog before and after the experimental production of hypothyroidism by the use of I^{131}.

METHODS

Blood flow in the coronary sinus was measured by the nitrous oxide desaturation method as described by Goodale et al.[4] Cardiac output, arterial blood pressure, left ventricular oxygen consumption, etc., were measured or calculated by methods described earlier.[5] The protein bound iodine (PBI) conversion ratio was estimated by using an anion exchange resin to remove iodide I^{131}.

The observations were made under morphine chloralose anesthesia on a series of fourteen dogs weighing 17 to 24 kg. The routine experimental procedure for all of the dogs consisted of two sets of observations on each dog on the same day, the two experiments being separated by an interval of about one hour. During this period depth of anesthesia and other factors were kept as nearly constant as possible. This approach (double runs) was applied to the following experimental categories: (1) "normal" dogs, (2) normal followed by atropine, (3) dogs with hypothyroidism, (4) hypothyroid followed by atropine. The dosage of atropine was 0.2 mg. per kg. given intravenously. A few days after the normal experiment the dog was given 30 to 35 mc. I^{131} by stomach tube. Four to eight weeks later a second "double run" was performed, i.e., the same measurements were repeated both before and after administration of I^{131}.

RESULTS

Table 1 lists the average values of the data in the "normal" and in the hypothyroid state both before and after the administration of atropine. The average per cent change for the several categories is also listed. It is important to note that the per cent change is calculated for each individual difference and then averaged, i.e., the calculation of per cent was based on the average of the differences, not on the difference of the averages. P value for the average per cent change of several factors considered to be of special interest is also included.

* From the Department of Physiology and the Institute for Cardiovascular Research, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania. This study was supported by Grant No. H-3815 of the National Heart Institute, U. S. Public Health Service.

TABLE I
Mean and Average Per Cent Change of Measured Values

Factors*	Group (1) Normal	(2) Hypothyroid	(3) Average Per Cent Change of Groups (1) to (2)	(4) Normal plus Atropine	(5) Average Per Cent Change of Groups (1) to (4)	(6) Hypothyroid plus Atropine	(7) Average Per Cent Change of Groups (2) to (6)
No. of cases	13	14	14	11	11	14	14
CSBF	61.7	43.3	−27 p<0.001†	122	+99	121	178
CVR	1.8	2.6	+47	1.1	−37	1.2	−51
MABP	110	105	+0.7	128	+10	135	+27
CI	2.2	1.5	−27 p<0.005	3.1	+48	2.0	+31
LVW	2.2	1.6	−27	3.7	+78	2.7	+78
LV O_2 cons.	8.46	5.8	−26 p<0.001	15.3	+79	15.1	+151
LV effic.	16.3	17.1	+14	16.4	−10	11.8	−34
HR	60	44	−19 p<0.005	229	+300	200	+354
A. O_2	21.2	20.5	−4	20.4	−6	18.9	−8
CS. O_2	7.2	6.9	−2	7.6	+5	6.4	−8
Cor. A-V O_2	14.0	13.2	−2	12.7	−7	12.8	−9
MRQ	0.81	0.78	+2	0.81	+2	0.88	+16
Systemic A-V O_2	7.06	7.32	+17.2 p<0.20	5.8	−26	7.0	−4
Rect. temp.	37.0	36.1	−5	37.3	+1	36.2	0
Respiratory rate	12	10	−11	16	+29	11	+4
Min. vol.	3.48	3.07	+3	4.8	+40	3.5	+25
BMR	43.1	31.4	−21 p<0.001	45.8	+1	33.0	+10

* CSBF = coronary sinus blood flow (100 ml. per 100 gm. per minute). CVR = coronary vascular resistance (MABP/CSBF). MABP = mean arterial pressure (mm. Hg). CI = cardiac index (L. per M^2 per minute). LVW = left ventricular work (kg. M. per minute). LV O_2 cons. = left ventricular oxygen consumption (ml. per 100 gm. per minute). LV effic. = left ventricular efficiency (%). HR = heart rate. A.O_2 = arterial oxygen, volumes per cent. CS. O_2 = coronary sinus blood oxygen, volumes per cent. Cor. A-V O_2 = coronary arteriovenous oxygen difference. MRQ = myocardial respiratory quotient. Systemic A-V O_2 = systemic arteriovenous oxygen difference. Rect. temp. = rectal temperature, degrees C. Min. vol. = respiratory minute volume (L. per minute). BMR = basal metabolic rate (calories per M^2 per minute).

† p = probability of value being due to chance.

Effects of I^{131}: The average protein bound iodine conversion ratio of ten dogs following administration of I^{131} was 3.9 per cent. The average basal metabolism rate of the dogs after I^{131} was 31 calories per M^2 per hour compared to a normal value of 43 calories, a decrease of 21 per cent. These two findings were taken as evidence of a hypothyroid state.

Effects of Hypothyroidism on Circulation: Marked decreases occurred in coronary sinus blood flow, cardiac index, left ventricular oxygen consumption, left ventricular work and heart rate. Increases occurred in coronary vascular resistance, systemic A-V oxygen difference and respiratory minute volume. The ratio of *left ventricular oxygen consumption/body oxygen consumption* was 0.055 in the normal and 0.053 in the hypothyroid group.

Effects of Atropine on the Normal Dog: These effects were similar to those previously observed[5] but were repeated in this study in order to follow the same dog from the normal to the hypothyroid state. Coronary sinus blood flow, cardiac index, left ventricular work and oxygen

consumption, heart rate, respiratory rate and respiratory minute volume showed marked increases.

Effects of Atropine on the Dog with Hypothyroidism: The increases noted previously also occurred in the animal with hypothyroidism. The absolute values for coronary sinus blood flow and heart rate were approximately the same but since the pre-atropine values were smaller the percentage change with atropine was greater in the hypothyroid. Both the absolute and percentage change in cardiac index were somewhat smaller. A considerably greater reduction in calculated left ventricular efficiency was produced by atropine in the dog with hypothyroidism again as a result of the higher efficiency in the pre-atropine state.

Comments

Heart Rate: The increase or decrease in heart rate associated with hyperthyroidism or hypothyroidism, respectively, has been attributed to the specific effects of the thyroid hormones on the myocardial tissue. Thyroxine accelerates the rate in perfused hearts[6] or even in the embryonic heart before the development of neural tissue.[7] In our experiments the per cent increase in heart rate following atropine was greater in the hypothyroid than in the normal group but the actual rates in the two groups were approximately the same. The reduction in heart rate with hypothyroidism appears to be associated with an increased vagal tone or possibly with a reduction in the threshold to vagal stimulation, since the blocking of vagal activity with atropine produced similar heart rates in both groups. If one considers atropine in the dosage used in these experiments as a stress stimulus, the hypothyroid heart seems to have lost little of its rate-adaptive capacity. This is significant because the ability of the heart to change its rate is an important cardiac reserve mechanism.

Myocardial Oxygen Consumption: Both the total body oxygen consumption and the left ventricular oxygen consumption were reduced in the hypothyroid state. A comparison of the ratio of left ventricular to body oxygen consumption in the normal with the hypothyroid group failed to show a significant difference. This is in agreement with Light et al.,[8] who noted a proportional increase in myocardial oxygen consumption in clinical hyperthyroidism. Since the influence of the thyroid upon myocardial oxygen consumption has been demonstrated with cardiac tissue slices,[9] it might be assumed that the regulation is primarily at the cellular level rather than by means of heart rate. On the other hand, the regulation in the intact animal may be effected to a significant degree through control of the heart rate. Recent evidence strongly supports the close association between myocardial oxygen consumption and heart rate in the dog in a variety of experimental situations.[5,10,11]

This relationship also is borne out in the present data by the results obtained when atropine was given to the normal and to the hypothyroid dog. Here there were extreme increases in heart rate associated with marked increases in myocardial oxygen consumption. In the hypothyroid state the oxygen consumption of the left ventricle increased over 150 per cent in association with a 350 per cent increase in rate. The important point, however, is that the relatively low oxygen consumption of the hypothyroid heart equaled the value of the normal group when both were subjected to the influence of atropine. Thus the influence of rate upon left ventricular oxygen consumption appears to be of the same order of magnitude in the hypothyroid and the normal heart under these experimental conditions.

Coronary Sinus Blood Flow: The changes in coronary sinus blood flow paralleled those for left ventricular oxygen consumption. The flow decreased in the hypothyroid state and increased with atropine in both groups, reaching about the same value in spite of starting at a lower level in the hypothyroid group. Again the explanation rests on the evidence of a close association between coronary flow and heart rate.[5,10,11]

Cardiac Index: The reduction in cardiac index in the hypothyroid dog agrees with the findings of Stewart et al.[2] in patients with myxedema. They also reported an increase in the systemic A-V oxygen difference which was associated with an increase in circulation time. Although not statistically significant, the increase in A-V oxygen difference is present in our data also and probably indicates correctly the direction of change. This increase should be considered in relation to the total body oxygen consumption. The decrease in cardiac index is associated with a decrease in total oxygen consumption but an increased A-V oxygen difference. Since

$$\text{A-V } O_2 \text{ difference} = \frac{\text{oxygen consumption}}{\text{cardiac output}}$$

it appears that the cardiac index decreased rela-

tively more than the oxygen consumption or, that the oxygen consumption was maintained in the hypothyroid at the expense of an increased A-V oxygen difference. This state is referred to as class 2 (a) in a previous publication.[5] Atropine increased the cardiac index and decreased the systemic A-V oxygen difference in both the normal and the hypothyroid animals but here also the cardiac index remained at a lower level and the A-V oxygen difference was consistently higher than in the normal group.

The lower cardiac index in the dog with hypothyroidism is due to either a reduction in the contractile strength of the myocardium or to a raised threshold to stimuli which increase the cardiac output. Evidence from our experiments can not differentiate between these two possibilities although all of the experimental procedures for the normal and the hypothyroid dogs were as nearly identical as possible. Studies[6] demonstrating an increased cardiac output in the perfused heart with thyroid substances suggest that the former explanation is more likely to be the correct one.

Summary

A reduction in the basal metabolism rate and protein bound iodine conversion ratio in a group of dogs following the administration of I^{131} was accepted as evidence of experimentally induced hypothyroidism. Observations of cardiac functions were made in the normal control group and in the hypothyroid group. The latter group was characterized by a reduction in coronary sinus blood flow, left ventricular oxygen consumption and heart rate. Atropine increased each of these values in the hypothyroid animals to a level approximately equal to that induced by atropine in the normal control group. The ability of the hypothyroid heart to raise coronary sinus blood flow and left ventricular oxygen consumption to the level of the normal heart in response to atropine is explained in terms of changes in heart rate because a close association between heart rate and these two functions has been established under a wide variety of experimental conditions. The capacity of the hypothyroid heart to change its rate appears to be unimpaired.

The cardiac index of the hypothyroid heart is also reduced but fails to return to the normal control levels in response to atropine. This reduction is probably associated with an increase in A-V oxygen difference, indicating a relatively greater reduction in cardiac output than in total oxygen consumption.

Acknowledgment

We wish to express our appreciation to L. Miller for his technical advice and assistance.

References

1. Andrus, E. The thyroid and the circulation. *Circulation*, 7: 437, 1953.
2. Stewart, H. J., Deitrick, J. E. and Crane, N. F. Studies of the circulation in patients suffering from spontaneous myxedema. *J. Clin. Invest.*, 17: 237, 1938.
3. The Physiology of Induced Hypothermia, p. 146. Edited by Dripps, R. D. Washington, D. C., 1956. National Academy of Sciences, National Research Council.
4. Goodale, W. T. and Hackel, D. B. Measurement of coronary blood flow in dogs and man from rate of myocardial nitrous oxide desaturation. *Circulation Res.* 1: 502, 1953.
5. Scott, J. C. and Balourdas, T. A. An analysis of coronary flow and related factors following vagotomy, atropine and sympathectomy. *Circulation Res.*, 7: 162, 1959.
6. Kleinfeld, M., Rosenthal, A. and Stein, E. Comparative effects of DL-thyronine, L-triiodothyronine and L-thyroxine on the isolated perfused frog heart. *Am. J. Physiol.*, 195: 63, 1958.
7. Markowitz, C. and Yater, W. M. Response of explanted cardiac muscle to thyroxine. *Am. J. Physiol.*, 100: 162, 1932.
8. Light, L., DeFazio, V., Talmers, F. N., Regan, T. R. and Hellems, H. K. Coronary blood flow, myocardial oxygen consumption and myocardial metabolism in normal and hyperthyroid human subjects. *Circulation*, 14: 90, 1956.
9. Goh, K. O. and Dallam, R. D. Oxygen consumption of the auricles, right and left ventricles of the normal hypothyroid and hyperthyroid rat heart. *Am. J. Physiol.*, 188, 514, 1957.
10. Scott, J. C. and Balourdas, T. A. Effect of atropine and of chronic A-V block on coronary blood flow in the dog. *Am. J. Physiol.*, 198, 145, 1960.
11. Laurent, D., Williams-Bolene, C., Williams, F. L., and Katz, L. N. Effects of heart rate on coronary flow and cardiac oxygen consumption. *Am. J. Physiol.*, 185: 355, 1956.

Effect of Reserpine on Tachycardia Induced by Thyroid in the Isolated Atrium of the Rat*

IRWIN E. MENDELSOHN, M.D., ARTHUR BASSETT, JOHN J. KELLY, JR., M.D.† *and* BRIAN F. HOFFMAN, M.D.

Brooklyn, New York

TACHYCARDIA IS A COMMON manifestation of thyrotoxicosis; similarly, administration of thyroid hormone causes an increase in heart rate. However, it is uncertain whether these changes in heart rate are from a direct action of thyroid hormone on the cardiac pacemaker or are brought about by an effect of thyroid hormone on either the sensitivity of the heart to catecholamines or on the catecholamine content of the heart. Several studies have suggested that thyroid hormone does indeed cause sensitization of the cardiac pacemaker to epinephrine.[1,2] Also, it has been demonstrated that in isolated perfused hearts thyroid extract does not increase rate.[3,4] This problem has been studied using atria isolated from normal and hyperthyroid rats, some of which had been treated with reserpine to deplete the catecholamine content of cardiac tissues.[5,6]

METHOD

Forty-nine young male albino rats (Wistar strain) of comparable size and age were divided into four groups. Twelve animals did not survive until completion of the experiment or could not be used because of technical difficulties. The animals were kept in clean, temperature controlled cages and were fed Purina laboratory chow and tap water. Oxygen consumption was determined by the method of Levey,[7] employing an airtight respirometer containing soda lime connected to a 50 ml. burette which stands inverted in a beaker of water. An oxygen inlet tube and thermometer are attached to the cover of the chamber. The inverted burette acts as one limb of a water manometer. The burette markings record changes in pressure rather than volume. A constant for the volume of the chamber was determined for each respirometer by noting pressure changes in the burette after injection of known volumes of air.

Rats were weighed and placed in the respirometer. The chamber was covered with cloth to quiet the animals and the system filled with 100 per cent oxygen. The difference between the initial burette reading and a reading five minutes later was recorded. This determination was multiplied by the constant of the respirometer volume and by 12 to give the oxygen consumed per hour. The product was then corrected for temperature and barometric pressure and divided by the surface area of the animal. The oxygen consumption was expressed as ml. oxygen per 100 cm.^{2} per hour. Determinations of oxygen consumption were repeated at intervals of several days until consistent values were obtained for each animal.

Two groups of animals (A and B) were fed thyroid powder (4 gm. per kg. dry food). Administration of thyroid was continued until the animal was sacrificed. One of the groups (B) which had been fed thyroid and one control group (C) were given an intraperitoneal injection of reserpine (0.1 mg. per 100 gm. body weight) daily for three days prior to being sacrificed. The fourth group (D) served as an untreated control. The parameters used to gauge the degree of hyperthyroidism were as follows: (1) an increase in basal metabolic rate (average 81 per cent), (2) a loss of weight, and (3) increased irritability. Animals treated with thyroid were sacrificed when they fulfilled these criteria. There were seven rats each in groups A and B, ten in group C and thirteen in group D.

Atrial Preparation: To determine the atrial rate in the isolated preparation the heart was removed rapidly under ether anesthesia and dissected in oxygenated, modified Tyrode's solution[8] at room temperature. Ventricular muscle, fat, blood vessels and connective tissue were detached from the right atrium and sinus node. After trimming, the atrium and node were mounted in a muscle holder. The tip of the atrial appendage was tied with thread which was then connected to the recording device (R.C.A. Transducer #5734). The muscle holder,

* From the Departments of Medicine and Physiology, State University of New York, Downstate Medical Center, Brooklyn, New York. Aided by a grant (H-1250) from the National Institutes of Health.

† Present address: Mercy Hospital, San Diego, California.

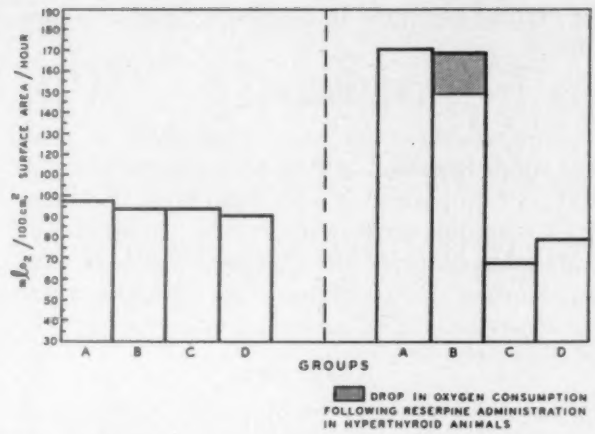


FIG. 1. Average oxygen consumption of rats in each experimental group; control values are on the left and final values on the right. Left, initial oxygen consumption. Average age of rats was eight weeks. Right, oxygen consumption after treatment with thyroid powder (group A), thyroid plus reserpine (group B) and reserpine (group C). Average age was fifteen weeks.

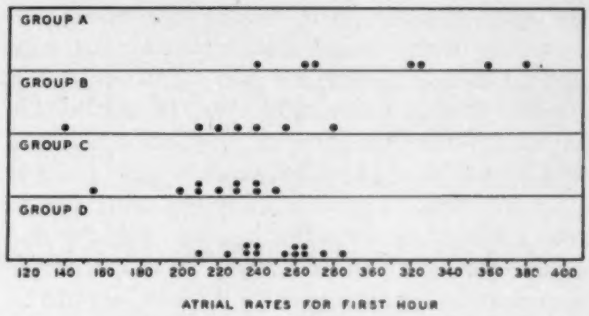


FIG. 2. Average atrial rate during the first hour after isolation of the atrium from each rat in each group.

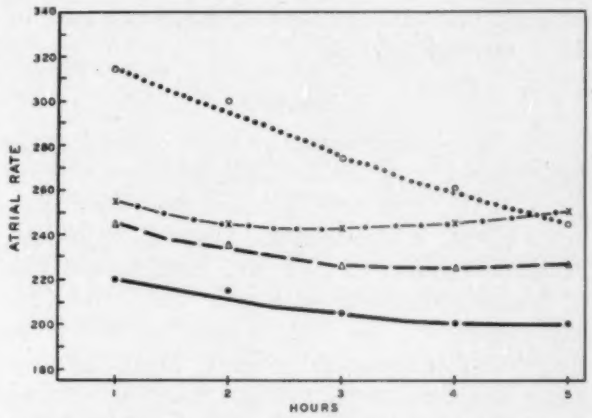


FIG. 3. Change in average atrial rate with time for rats from each experimental group. Group A, •••••• hyperthyroid; group B, Δ—— hyperthyroid plus reserpine; group C, •— reserpine control; group D, x—•— control.

chamber and transducer assemblage have been described previously.[8]

After mounting, the atrium was placed in the muscle chamber and perfused with modified Tyrode's solution at a rate of 4.5 ml. per minute. Temperature was maintained at 37° C. A mixture of 95 per cent oxygen and 5 per cent carbon dioxide was bubbled through the perfusing solution in the muscle chamber at a rate of 5 ml. per minute. The atria were held under resting tension of 2 gm. and contractions were recorded on a Sanborn oscillograph for periods of one and one-half to five and one-half hours.

RESULTS

The only group of animals which had a continuous weight gain throughout the experiment was the untreated control group (D). The control group treated with reserpine (C) showed a steady gain of weight until the beginning of administration of reserpine. Both groups fed thyroid powder (A and B) showed a marked inhibition of weight gain after the onset of thyroid feeding and each had an eventual loss of weight. In group B, the weight loss became most pronounced following administration of reserpine and averaged 36 gm.

The basal metabolic rate in all the groups prior to administration of drugs was remarkably constant and averaged 93 ml. oxygen per 100 cm.^{2} per hour (Fig. 1). Prior to being sacrificed, the basal metabolism of the control animals (C and D) had decreased to 72 ml. oxygen per 100 cm.^{2} per hour. This may be explained by the effect of aging on the basal metabolism.[9] The oxygen consumption of the hyperthyroid rats (A and B) rose to an average of 169 ml. oxygen per 100 cm.^{2} per hour or 81 per cent above the control level. After reserpine, a drop in basal metabolic rate of 11 per cent occurred (19 ml. O_2/100 cm.^{2} /hour) in group B.

The rates of the isolated atrial preparations are shown in Figure 2. The mean rate of atria from the control group (D) was 250 ± 18.8 beats per minute; atria from control animals given reserpine (C) averaged 218 ± 27.2 beats per minute. The mean atrial rate of hyperthyroid animals (group A) was 309 ± 51.6 beats per minute; in the hyperthyroid rats receiving reserpine (group B) the mean rate was 225 ± 43 beats per minute. It is important to note that reserpine administered *in vivo* brought the rate of the isolated atria back to the control range. Reserpine also seemed to cause a slight drop in the rate of atria in group C.

In the atria from rats in the control group (D)

the rate changed little during five hours observation in the muscle holder; in both groups treated with reserpine (B and C), the rate fell slightly in five hours (Fig. 3). In the hyperthyroid group (A), however, not only was initial rate higher but also there was a sharper decline until it reached approximately the same rate as that attained by atria from group D at the end of five hours. The similarity in shape of the curves obtained from groups B and C should be noted.

These studies did not reveal a constant relationship between the magnitude of increase in heart rate and the level of metabolic rate in the hyperthyroid rats.

Comments

The tachycardia seen in atria isolated from hyperthyroid rats can be prevented by pretreatment with reserpine (group B). The primary effect, in this instance, appears to be the peripheral action of reserpine causing the loss of sympathomimetic substance from the cardiac tissue.[5,6] The fall in rate of group A (hyperthyroid animals) over a period of five hours suggests either a gradual loss of something from atrial myocardium in this group which is present in excess only in group A, or a sensitivity of atria in group A to a substance which is present in the same amount in all atria but does not influence the rate of groups other than A. It is our belief that this work lends further support to the theory which ascribes increased sensitivity to catecholamine as the main effect of thyroid hormone in causing cardiac acceleration.

Summary

Isolated rat atria have been used to study the mode of action of thyroid hormone on heart rate. Comparison of atria from normal control, hyperthyroid and reserpinized hyperthyroid rats demonstrates the probable role of catecholamines in mediation of thyroid-induced tachycardia.

References

1. Levy, R. L. The effect of thyroid secretion on the pressor action of adrenine. *Am. J. Physiol.*, 41: 492, 1916.
2. Goetsch, E. Newer methods in the diagnosis of thyroid disorders: pathological and clinical. *New York J. Med.*, 18: 259, 1918.
3. Andrus, E. C. The heart in hyperthyroidism. A clinical and experimental study. *Am. Heart J.*, 8: 66, 1933.
4. Lewis, J. K. and McEachern, D. Persistence of an accelerated rate in the isolated hearts and isolated auricles of thyrotoxic rabbits. *Bull. Johns Hopkins Hosp.*, 48: 228, 1931.
5. Bertler, A., Carlsson, A. and Rosengren, E. Release by reserpine of catechol amines from rabbits' hearts. *Die Naturwissenschaften.*, 22: 521, 1956.
6. Brodie, B. B., Olin, J. S., Kuntzman, R. G., and Shore, P. A. Possible interrelationship between release of brain norepinephrine and serotonin by reserpine. *Science*, 125: 1293, 1957.
7. Levey, H. A. Personal communication.
8. Hoffman, B. F. and Kelley, J. J. Effects of rate and rhythm on contraction of rat papillary muscle. *Am. J. Physiol.*, 197: 1199, 1959.
9. Fulton, J. E. A Textbook of Physiology, p. 1049. Philadelphia, 1955. W. B. Saunders Co.

QRS Alterations Produced by Auricular and Ventricular Paroxysmal Tachycardia in the Presence of Bundle Branch Block Patterns

An Experimental Study in Dogs*

OTTO F. MULLER, M.D., MANUEL CARDENAS, M.D. *and* SAMUEL BELLET, M.D., F.A.C.C.

Philadelphia, Pennsylvania

THE QRS COMPLEXES IN ventricular tachycardia are usually considered to present a configuration characterized by an increased width.[1-3] It is well known that widened QRS complexes, on the other hand, are not necessarily of ventricular origin, many of them arising from a supraventricular focus and exhibiting various degrees of aberration. In these conditions it is often difficult to identify the auricular complex, making the differential diagnosis between supraventricular and ventricular complexes difficult.[4] Moreover, the presence of a paroxysmal tachycardia composed of QRS complexes of normal width has usually been ascribed to a supraventricular or nodal origin.

The occurrence of premature ventricular beats, when the QRS complexes manifest a narrowing or relatively normal width as compared to the control tracing, has been observed but little studied.[5-9] The site of origin of such ectopic beats has been described (1) in the main stem of the bundle of His[10-12] and (2) in the upper portion of the interventricular septum.[5,6,8,12] Narrow ventricular complexes were also thought to be due to a fortuitous resumption of an auricular focus activity.[13] Recently, it has been shown that ventricular extrasystoles with normal or slightly aberrant QRS morphology may be seen in the presence of complete bundle branch block patterns if the ectopic stimulus occurs during the P-R interval of the cardiac cycle. The studies of Bisteni et al.[14-16] relative to the site of origin of extrasystoles during sinus rhythm and in the presence of bundle branch block patterns are of considerable practical importance and have helped to fill in some of the gaps in the knowledge of this subject and to elucidate further the relationship between the site of origin and morphology of extrasystoles.

The following study was done in an attempt to determine the variations in the configuration and, in particular, the width of the QRS complexes in auricular and ventricular tachycardias from various sites of origin. These were investigated in the normal heart as well as following the production of partial and complete bundle branch block patterns. Data will be presented which will help define the site of origin of ventricular tachycardias with narrowed QRS complexes and will indicate that under certain circumstances they may arise in the free wall of the ventricle.

METHODS AND MATERIAL

Twenty healthy mongrel dogs weighing between 9 and 14 kg. were utilized for these experiments. The animals were anesthetized by intravenous injection of pentobarbital sodium (30 mg. per kg.). An intratracheal catheter was inserted and connected with a positive pressure breathing apparatus delivering compressed air at a rate of about fifteen respirations per minute. A femoral artery was cannulated for obtaining continuous arterial pressures by means of an electrical strain-gauge manometer. The pressures then were recorded together with an electrocardiogram on a multichannel Sanborn Polyviso electrocardiograph.

Surgical approach to the heart was either a right,

* From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pennsylvania. This work was supported by a grant from the U.S. Public Health Service, H141 (C-12), and the Eli Lilly Company, Indianapolis, Indiana.

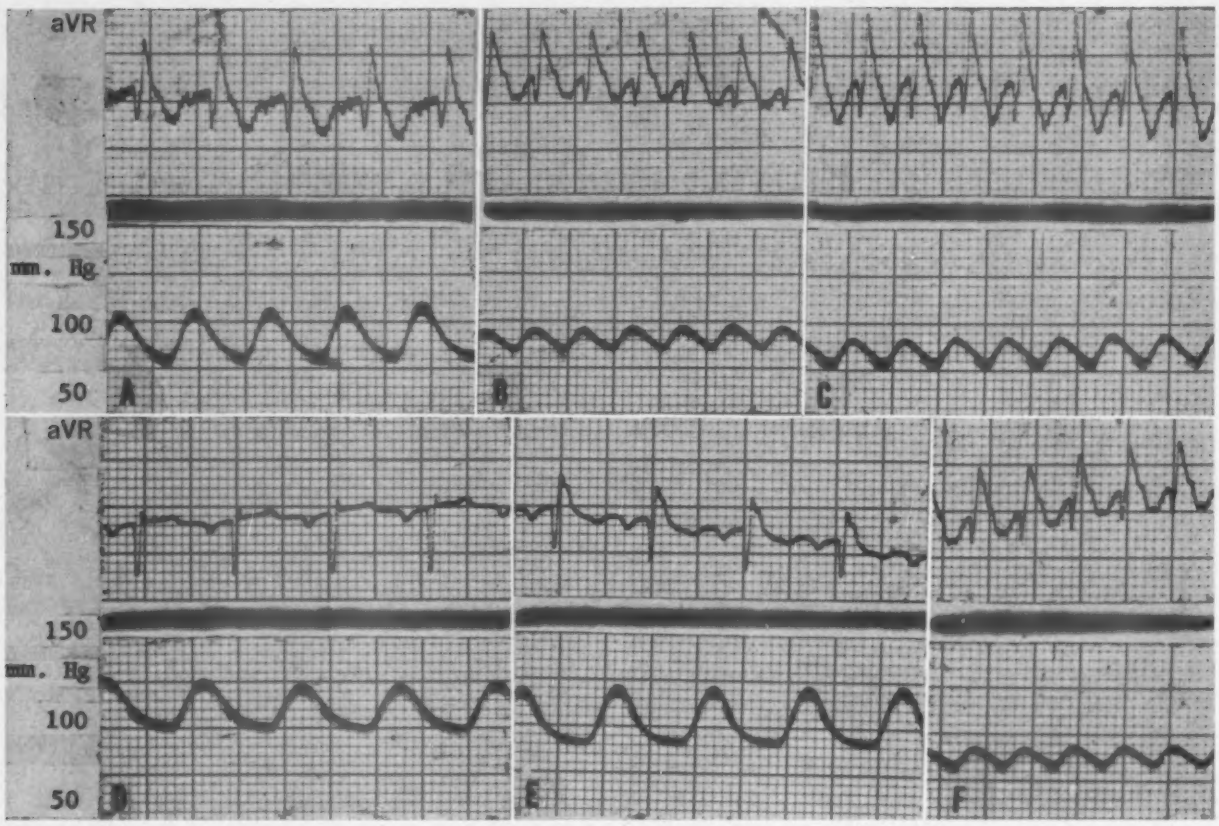


FIG. 1. QRS patterns of right auricular tachycardia and left ventricular tachycardia in the presence of complete and incomplete right bundle branch block. A, control tracing (aVR) after the production of complete right bundle branch block. QRS duration: 0.10 to 0.12 second. The tracing below shows simultaneous intra-arterial blood pressure recording. B, following the production of right auricular tachycardia (rate 290 per minute). QRS duration: 0.10 to 0.12 second. Note the similarity of QRS to that in (A). C, paroxysmal ventricular tachycardia due to an ectopic focus in the free wall of the left ventricle (rate 275 per minute). QRS duration: 0.10 second. D, control tracing (aVR). QRS duration: 0.05 second. E, after production of incomplete right bundle branch block (rate 150 per minute). QRS duration: 0.09 second. F, after production of auricular tachycardia (rate 290 per minute). QRS duration: 0.12 second.

left or transsternal thoracotomy at the level of the third interspace. The choice depended upon the type of bundle branch block or tachycardia contemplated. Ventricular tachycardia was produced from various sites of origin in the right or left ventricular wall as follows: (1) in the normal dog; (2) after the production of complete or partial left and right bundle branch block; and (3) in the presence of complete A-V heart block.

Production and Termination of the Tachycardias: Auricular and ventricular tachycardias were induced by a method previously employed by various investigators.[17,18,19] The myocardial surface was dried thoroughly and small cotton applicators saturated with 0.5 per cent solution of aconitine crystals in benzine were pressed to either the auricular or ventricular myocardium for five to fifteen seconds. The onset of the tachycardia was always slow and spontaneous remissions to slower rates occurred frequently.

One per cent procaine or lidocaine (Xylocaine®) solution was injected in minute amounts into the myocardial site of the former application of aconitine to terminate the various tachycardias. This procedure promptly stopped the paroxysmal tachycardia with a return of the original QRS patterns and heart rate. We found this method quicker and more reliable than cooling the site of application of aconitine with ice or spraying it with ethyl chloride.[17,18]

In some instances a ventricular tachycardia was produced from a focus in one ventricle and when the rhythm had become stable a second aconitine focus was induced in the other ventricle in order to study the combined effects of these tachycardias on the electrocardiogram. Xylocaine was injected alternately in the two sites of origin in order to control and confirm the individual and combined sites of origin on the electrocardiogram.

Production of Bundle Branch Block: The technic for the sectioning of the branches of the bundle of His was similar to that described by Sodi-Pallares, Rodriguez et al.[20–22] Upon opening the pericardium, a sharp, straight needle was introduced through the

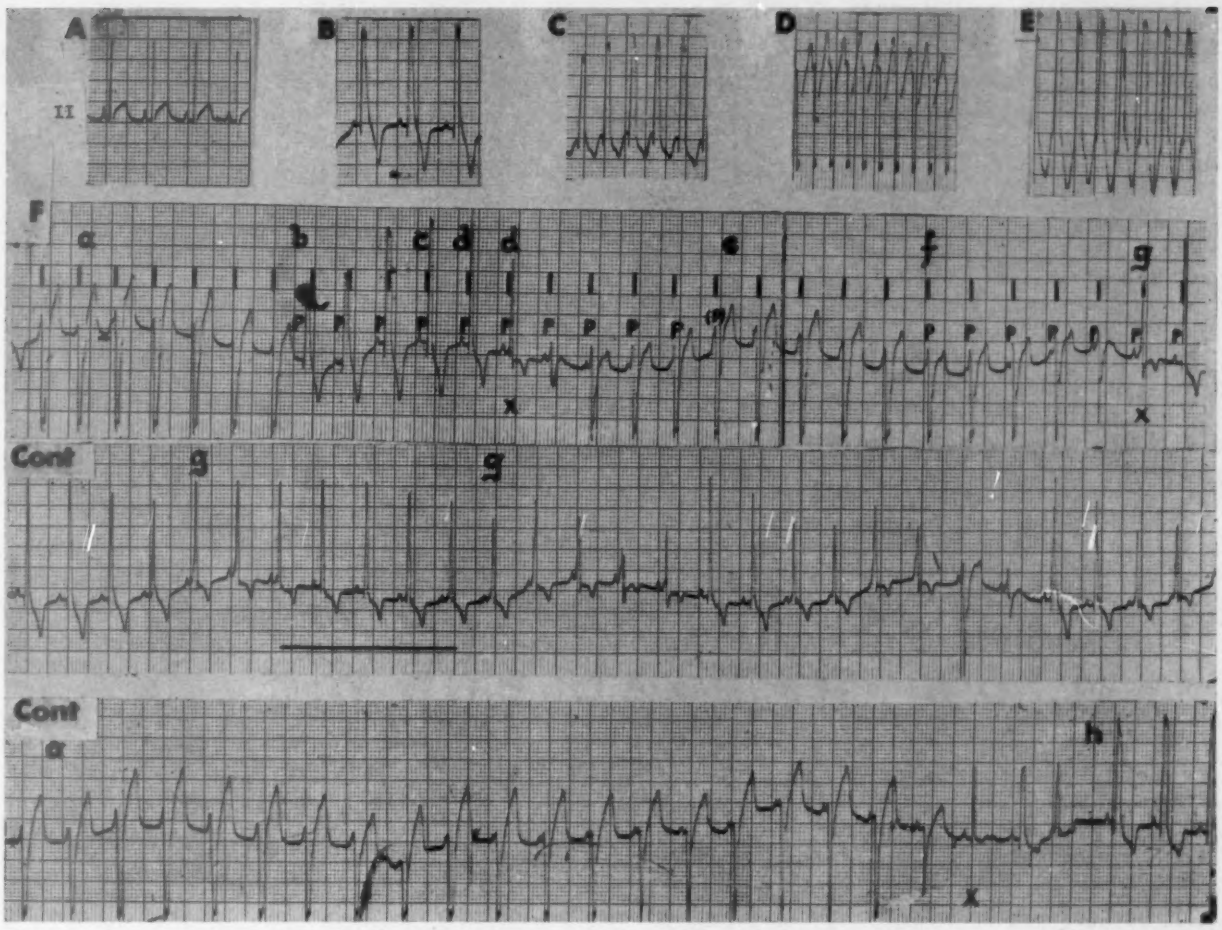


FIG. 2. The effect of tachycardias from various sites upon the QRS in the presence of left bundle branch block (for detailed explanation, see text). A, control tracing (lead II). QRS duration: 0.04 second. B, after production of left bundle branch block. QRS duration: 0.12 second. C, left auricular tachycardia. QRS duration: 0.10 to 0.12 second. D, left ventricular tachycardia. QRS duration: 0.08 to 0.10 second (right bundle branch block pattern). E, right ventricular tachycardia. QRS duration: 0.10 second. Note the similarity of this tracing to (C). F, left ventricular tachycardia (a) in the presence of supraventricular tachycardias with left bundle branch block (b, h). Fusion beats with narrowed QRS complexes of various configurations occur (c, d, g) depending upon the part of the cardiac cycle, or more specific, the P-R interval, into which the ectopic stimuli of the left ventricle fall. If left ventricular activation occurs immediately after the P wave, Wolff-Parkinson-White–like patterns are produced (g). The second strip of the tracing represents a continuous run of fusion beats. In other words, ventricular tachycardia is present.

free wall of either the right or left ventricle just below the atrioventricular junction. The point of the needle was directed towards the region where the bundle branches emerge in the interventricular septum (the septal portion under the tricuspid valve for the right branch; and under the aortic semilunar valve between the posterior and left cusps for the left branch).[20] The bundles were cut completely or partially, as desired, by a few dorsal-ventral movements of the needle tip. Electrocardiographic monitoring was utilized to determine the success of the procedure.

Leads aVR and II were used to monitor right and left bundle branch block, respectively.[22,23] Before proceeding to the next part of the experiment, the maintenance of the bundle branch block patterns was observed for ten to fifteen minutes.

Production of Complete A-V Heart Block: In four dogs complete A-V heart block was produced to eliminate the interference of auricular with ventricular activity, when tachycardias from both ventricles were induced. For this purpose 2 to 4 cc. of 10 per cent formaldehyde solution (formalin) were injected into the A-V nodal region, approaching it through the right auricle according to the technic described in a previous paper from this laboratory.[24]

RESULTS

The Effect of Supraventricular Tachycardia upon the QRS of Bundle Branch Block Patterns: In dogs with various degrees of right (five dogs) and left bundle branch block (five dogs), paroxysmal supraventricular tachycardias were pro-

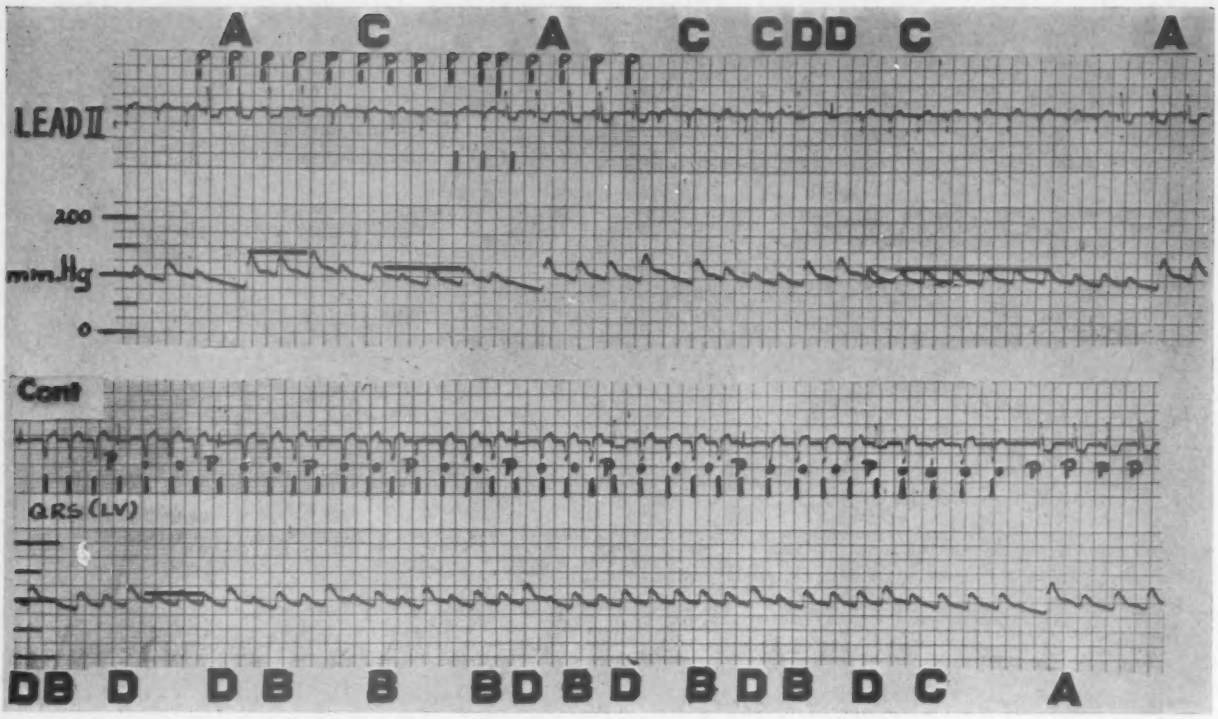


FIG. 3. Left ventricular tachycardia in the presence of left bundle branch block. This is a continuous tracing of lead II with simultaneous intra-arterial blood pressure recording. A, left bundle branch block. QRS duration: 0.08 second. The dominating rhythm is supraventricular. B, left ventricular complexes which fall into the responsive period of the cardiac cycle (between end of T and beginning of P). QRS duration: 0.08 second. Because the rate of the ectopic focus is faster than the supraventricular one, the dominating rhythm is left ventricular tachycardia. C, left ventricular complexes which occur on or immediately after the P wave. QRS is narrowed (0.04 to 0.06 second) but the direction of inscription is like that of the original left ventricular complex since left ventricular activation starts slightly earlier than right ventricular activation. D, left ventricular complexes occurring late during the P-R interval fuse with the supraventricular activation wave through the right bundle branch and render narrow QRS complexes which resemble the normal pattern before production of left bundle branch block. QRS duration: 0.04 second. Note the blood pressure responses: supraventricular beats (A) yield the highest systolic response (140/100 mm. Hg). It is lower in fusion beats (C and D) (120/100 mm. Hg) and decreases slightly more if the left ventricular focus (B) gives rise to cardiac contraction (110/90 mm. Hg).

duced from an aconitine focus in the right atrial appendage. There is no significant modifying effect on the QRS pattern of either right (Fig. 1A and B) or left bundle branch block. This is in line with what one would anticipate because ventricular depolarization occurs in the same manner as in the control. In the incomplete types of bundle branch blocks the control QRS width (0.08 second) increases (0.12 second) following the production of auricular tachycardias incident to the higher rate and fatigue of the partly injured bundle branch (Fig. 1D, E and F). Following the abolition of the aconitine focus the electrocardiogram returned to the control pattern.

The Effect of Left Ventricular Tachycardia on the QRS in the Presence of Right Bundle Branch Block: If a paroxysmal tachycardia were produced in the free wall of the left ventricle in the presence of right bundle branch block, the morphology of the QRS during the ventricular tachycardia resembled the control pattern with right bundle branch block (Fig. 1C). The explanation is obvious because activation of the left ventricle occurs first, as in right bundle branch block. The delay in activation follows the same mechanism in both right bundle branch block and in left ventricular tachycardia, as will be discussed. When the auricular rate is high and the P wave inscriptions are not discernible, it is often impossible to differentiate supraventricular tachycardia with bundle branch block from ventricular tachycardia arising in the contralateral ventricle (Fig. 1B and C). The same findings were observed when right ventricular tachycardia was produced in the presence of left bundle branch block (Fig. 2C and E).

The Effect of Left Ventricular Tachycardia on the QRS in the Presence of Left Bundle Branch Block: If, in the presence of left bundle branch block, a

ventricular tachycardia were produced in the free wall of the left ventricle, the electrocardiogram showed various patterns. These patterns depended upon the automatic center which determines ventricular activity at the particular instant and also upon the time in the cardiac cycle in which the ectopic ventricular stimulus falls. The following patterns were observed:

A. If the ectopic stimulus occurs during the absolute refractory period the electrocardiogram remains unchanged because the stimulus fails to produce a ventricular response (see points A in Fig. 3). The dominant rhythm is supraventricular with left bundle branch block.

B. If the ectopic impulse falls into the responsive period of the cardiac cycle between the end of T and the beginning of P, a right bundle branch block pattern (left ventricular extrasystolic pattern) is produced. The P waves are not discernible and the QRS complexes are widened (see points B in Fig. 3.). If the rate of the ectopic focus is faster than that of the supraventricular focus, the dominant rhythm is left ventricular tachycardia.

C. If, however, the ventricular stimuli occur within the P-R interval of the cardiac cycle, fusion beats result with normal or only slightly aberrant QRS complexes. The morphology of these complexes depends more specifically upon the part of the P-R interval into which the ectopic stimulus falls. When the activation of the left ventricle is initiated on or shortly after the P wave, the resulting complexes are narrow and the main QRS deflections follow those of the ventricular extrasystoles. This is to be expected because activation of the left ventricle occurs slightly earlier than that of the right ventricle (see points C in Fig. 3). When, on the other hand, the ventricular stimulus falls late in the P-R interval the sequence of activation closely resembles that of normal ventricular activation and the QRS pattern becomes more and more similar to the original tracing; that is, the one present before the bundle branch block was produced (see points D in Fig. 3).

Supraventricular beats yielded the highest blood pressure responses (e.g., 140/100 mm. Hg). Fusion beats led to a drop in blood pressure (e.g., 120/90 mm. Hg) which usually was more marked in pure ventricular beats (e.g., 110/90 mm. Hg) (Fig. 3). .

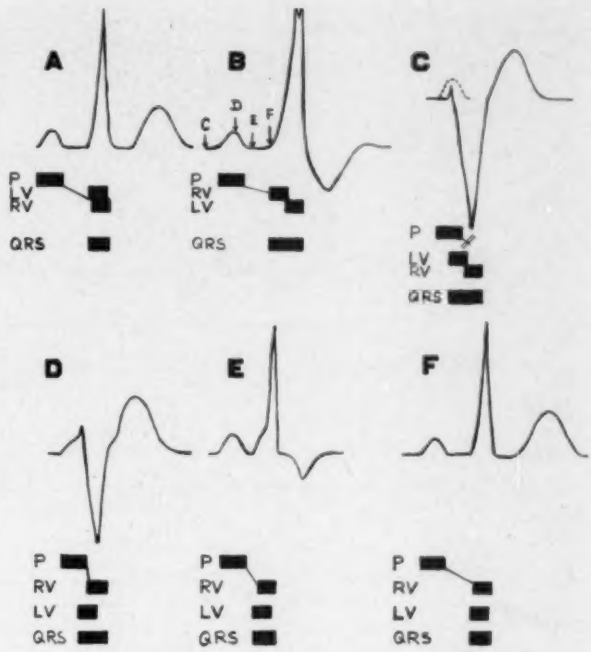


FIG. 4. Diagrammatic representation of various possibilities in conduction. A, normal complex, lead II. B, left bundle branch block pattern in lead II. The succession of events in the various chambers is noted in block form below. The activation wave travels from the auricles to the right ventricle; delay occurs in the barrier zone of the septum before the left ventricle is activated. C, left ventricular extrasystole. The left ventricle is activated first; after occurrence of the conduction delay in the septal zone, activation of the right ventricle takes place. The QRS is widened and aberrant, as in right bundle branch block. D, R wave of ventricular complex starting on the peak of the P wave. Immediately after the activation of the auricles has begun, the left ventricular events start. The main QRS deflection, therefore, is like that of the left ventricular extrasystole. E, left ventricular activation occurs immediately after the P wave. Wolff-Parkinson-White–like complexes occur (short P-R interval, widened QRS and delta wave). F, left ventricular extrasystole at the beginning of the QRS complexes. P is conducted to the right ventricle. At the same time the left ventricular events take place, so that the over-all activation of the heart resembles closely normal activation without bundle branch block. The P-QRS complex is inscribed in a normal fashion, or only slightly aberrant. If the extrasystolic focus falls between D and E, narrowed complexes with changing morphology appear.

Figure 2 demonstrates the effect of tachycardias from various foci on the QRS pattern in the presence of left bundle branch block. *A* is the control tracing (lead II). In *B* complete left bundle branch block has been produced. *C* shows the effect of supraventricular tachycardias. The QRS pattern is unchanged. *D* represents left ventricular tachycardia, the QRS exhibiting the pattern of right bundle branch block. *E* has been recorded during right ventricular tachycardia which manifests a left bundle branch block pattern. This pattern is similar to that of supraventricular tachycardia in the presence of left bundle branch block (Fig. 2C).

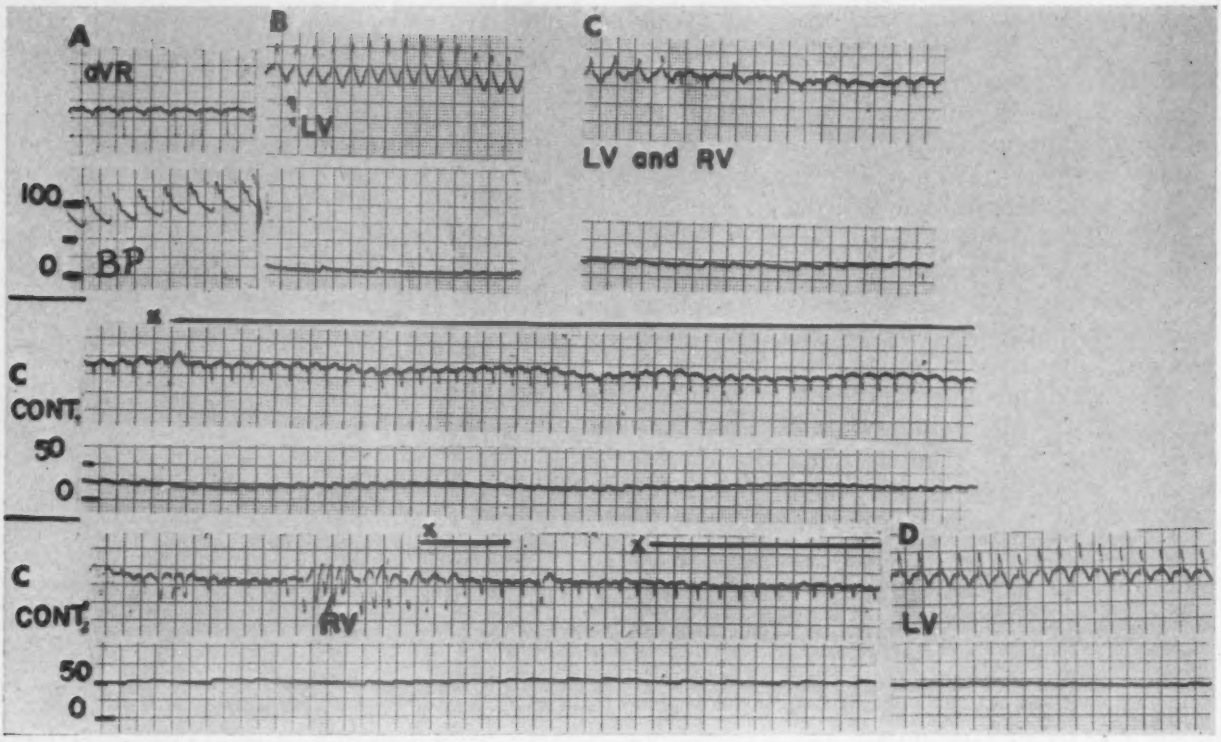


FIG. 5. Left and right ventricular tachycardia with normal sinus rhythm. A, control tracing (aVR). B, left ventricular tachycardia. C, biventricular tachycardia. Note long runs of biventricular tachycardia with narrowed QRS complexes (fusion of two activation waves) at X. D, left ventricular tachycardia is again present as soon as the right ventricular focus has been abolished by procaine injection into the site of the aconitine application.

In Fig. 2F, two foci compete in taking over cardiac rhythmicity, one supraventricular (sinus) and the other a left ventricular ectopic focus. The importance of the time relationship between the P-R interval and the ventricular stimulus relative to the resulting QRS morphology is clearly discernible. In the first strip, left ventricular tachycardia is the dominant rhythm (a) until a supraventricular beat falls into the nonrefractory period of the cardiac cycle (b). Now the supraventricular focus governs cardiac activity because the left ventricular foci fall into the refractory period. At (c), the ventricular focus begins to fall into the P-R interval, fuses with the supraventricular impulse and produces narrow beats (d) until left ventricular activation from the ectopic focus reaches the T-P interval and again takes over cardiac rhythmicity (e). This sequence is again shown in (f). At (g), left ventricular stimulation occurs immediately after the P wave. Since the ventricular complex in this experiment consisted of a small initial R and tall S waves, a Wolff-Parkinson-White–like pattern was produced (short P-R interval and widened QRS with a delta wave).

The second strip of *F* shows in sequence narrowed QRS complexes of varying configuration. All of these are fusion beats. In other words, ventricular tachycardia is present even in the presence of P waves preceding each QRS complex. At (a) on the third strip the ventricular focus is dominant again. After it is abolished by lidocaine (Xylocaine) injection, the supraventricular activity with left bundle branch block returns undisturbed (h, at end of third strip).

A similar sequence was observed with right ventricular tachycardia in the presence of right bundle branch block (this manifests a left bundle branch block pattern).

Figure 4 shows all of these possibilities graphically.

Biventricular Tachycardias: In a normal dog (control tracing, Fig. 5A), left ventricular tachycardia was produced first (Fig. 5B), then an ectopic focus was produced in the free wall of the right ventricle (Fig. 5C). After a period of competition between these two pacemakers, both stimuli occurred at approximately the same time and a biventricular tachycardia with narrow QRS complexes resembling the control tracing was seen (fusion beats; Fig. 5C).

Figure 5D shows a tracing of left ventricular tachycardia after the right ventricular focus has been blocked with intramyocardial xylocaine injection. Figure 6 depicts another experiment of this type.

Biventricular Tachycardia in the Presence of Complete A-V Heart Block: To eliminate the possi-

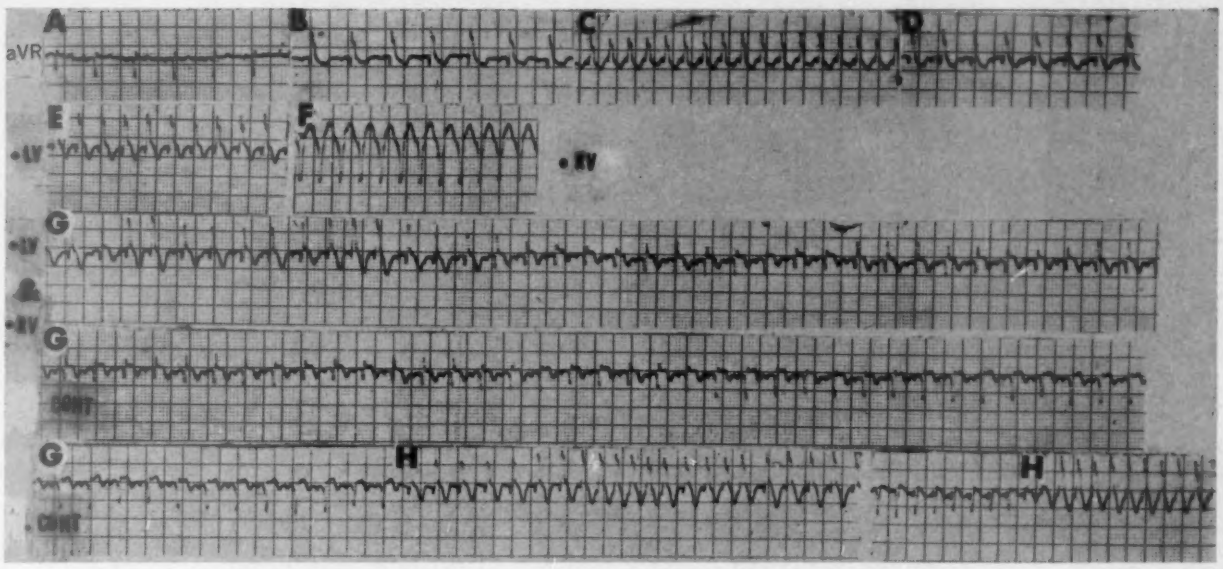


FIG. 6. Left and right ventricular tachycardia in the presence of right bundle branch block. A, control tracing (aVR): QRS duration: 0.04 second. B, after production of right bundle branch block. QRS duration: 0.08 second. C, right auricular tachycardia in the presence of right bundle branch block. QRS duration: 0.08 second. D, after abolition of the right auricular tachycardia by injection of lidocaine (Xylocaine) into the aconitine application site. QRS duration: 0.08 second. E, left ventricular tachycardia. Note again the similarity to right auricular tachycardia in C. F, right ventricular tachycardia. QRS duration: 0.07 to 0.08 second. G, biventricular tachycardia. Note long runs with narrowed QRS complexes which resemble closely the control tracing. After abolition of the right ventricular aconitine focus, the left ventricular tachycardia recurs (H).

bility of impulses coming from the auricles, one experiment was performed in a dog with complete A-V heart block. Figure 7 shows that the block initially appeared without aberration of the QRS complexes (Fig. 7B and C). Thereafter, an incomplete right bundle branch block was produced (Fig. 7D). When ectopic stimulation was applied to both ventricles, narrow normal-looking QRS complexes appeared frequently (complexes marked X, Fig. 7E and F). As soon as both ventricles contracted at a sufficient speed, runs of biventricular tachycardia with narrowed QRS complexes occurred (Fig. 7F). The dog subsequently died with terminal ventricular flutter and fibrillation.

Table 1 presents a summary of the QRS morphologies during paroxysmal tachycardias from various sites of origin in the presence of bundle branch block patterns. This table shows the relationship between the site of origin in the cardiac cycle of ectopic beats and the resultant morphologies of the QRS complexes in the presence of bundle branch block patterns.

COMMENTS

Rodriguez, Sodi-Pallares and associates[21,22] have recently shown that the fundamental abnormality in both left and right bundle branch block is an abnormally long delay in the passage of the activation wave from the intact to the affected side. This delay takes place in a relatively small zone at the junction of the left and right interventricular septal muscle masses. This zone acts as a barrier and it takes time for the activation wave to "jump" from one side to the other.[21] In the muscle mass of the interventricular septum itself (thick layer derived from the left ventricle and the thin right ventricular layer), the speed of the activation wave is unaltered in bundle branch block.[21,22,29]

The increase in duration of the QRS complex and its aberrant morphology in ventricular premature beats follow the mechanism of that found in bundle branch block.[22,25–28] In the case of an extrasystole from the free wall of the left ventricle, for instance, the activation wave in the left interventricular septal muscle mass was found equal to that of a normal stimulus.[27] The delay in the pathway and with it the increase in duration and aberration of the QRS complex occurs when the activation wave has to jump from the muscle fibers activated by the left branch to those activated by the right branch, as mentioned previously. Therefore, the activation pathway from the left ventricle resembles that of right bundle branch block. The same criteria hold for the extrasystoles arising from the right ventricle.

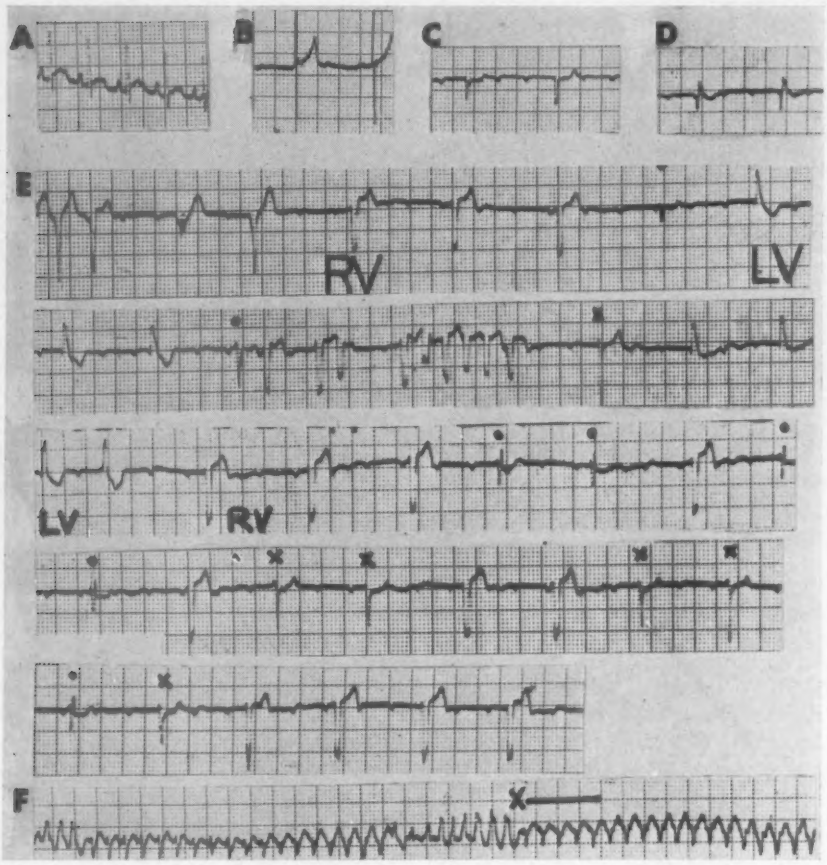


FIG. 7. The effect of simultaneous left and right ventricular tachycardia in a dog with complete A-V heart block. A, control tracing (lead II). B, after production of complete A-V block (lead II). C, complete A-V heart block recorded in lead aVR. D, since the QRS complex in the presence of complete A-V heart block did not show any aberrancy, an incomplete right bundle branch block was produced (aVR). E, production of ectopic aconitine foci in both ventricles (lead aVR). Note the occurrence of fusion beats with different morphology. At x the QRS resembles closely the control pattern before production of the incomplete bundle branch block (C). F, terminal biventricular tachycardia with narrowed QRS complexes (fusion between left and right ventricular tachycardia) at x.

It will follow from these observations that it may be extremely difficult to differentiate auricular tachycardia with right bundle branch block from left ventricular tachycardia or vice versa. Our experiments on the dog heart, as have been shown, confirmed these observations.

These findings differ markedly from the classic concepts of extrasystoles and make the following two hypotheses untenable: (1) that the widening and aberration of QRS complexes in ventricular extrasystoles is due to slow propagation of the impulse through the entire septum; and (2) that the impulse would ascend one branch and descend the other.[22]

Concerning ventricular extrasystoles arising at the site of the bundle branch block; Bisteni and associates[14–16] have shown that the morphology of the QRS complex depends on the time of the cardiac cycle in which the stimulus occurs.

In the nonrefractory period of the cardiac cycle between the end of the T wave and the beginning of the P, complete bundle branch patterns are produced. If the stimulus falls into the P-R interval, fusion beats of various morphologies occur. It has long been known that variform ventricular extrasystoles are particularly common in the presence of bundle branch blocks.[6,8,9] Experimentally, they were recorded when both bundle branches were severed or damaged.[30] We have observed multiform ventricular extrasystoles during cardiac catheterization when, in patients with complete right bundle branch block, the catheter tip

TABLE 1
Summary of QRS Morphologies during Paroxysmal Tachycardias in Presence of Bundle Branch Block

Ectopic Beat Discharged at the Following Portion of the Cardiac Cycle:	Resultant Morphology of QRS		
	If ectopic beats arise from supraventricular focus	If ectopic beats arise from ventricular focus	
		Right ventricle	Left ventricle
Between peak of P and beginning of QRS in LBBB*	LBBB	LBBB	Incomplete RBBB to normal (the closer to Q the narrower the QRS)
Between peak of P and beginning of QRS in RBBB†	RBBB	Incomplete LBBB to normal (the closer to Q the narrower the QRS)	RBBB
Between T and P in LBBB	Incomplete to complete LBBB	LBBB	RBBB
Between T and P in RBBB	Incomplete to complete RBBB	LBBB	RBBB

* LBBB = left bundle branch block; †RBBB = right bundle branch block.

encroached on the right ventricular endocardium.[31] From the observations in this study it can be followed that these multiform ventricular extrasystoles or runs of paroxysmal ventricular tachycardia may arise in one ventricular focus when it is located in the ventricle below the blocked bundle branch.

It is of particular interest that a ventricular stimulus which occurs during the P-R interval results in fusion with the supraventricular activation wave and therefore produces narrowed or relatively normal QRS complexes. Since the ventricle below the bundle branch block is activated almost at the same time as the other which receives its impulse from the auricle through the intact bundle branch, the cardiac activation will approach normal limits. The later the ventricular stimulus occurs during the P-R interval, the closer will the QRS complexes resemble a normal pattern.

It is of practical importance to note that complete bundle branch block patterns will be unaltered in supraventricular tachycardias; the QRS width of incomplete types, however, may be increased. Decrease in QRS duration during bundle branch block at the onset of the tachycardia may be the result of a superimposed ventricular tachycardia and presents a serious complication. A correct diagnosis is of great importance in these instances; appropriate drug therapy may be lifesaving.

The patterns of multiform ventricular extrasystoles and runs of paroxysmal ventricular tachycardias[31] observed in dogs were also encountered in human subjects during cardiac catheterization when the catheter tip, in patients with complete right bundle branch block, encroached on the right ventricular endocardium. Similar fusion beats and fusion types of ventricular tachycardia were also observed in human subjects during cardiac catheterization.

SUMMARY

Experimental auricular and ventricular tachycardias have been produced at various sites of the heart in the presence of bundle branch block. The following conclusions can be made:

1. Supraventricular tachycardias do not alter complete bundle branch block patterns significantly. They may, however, increase incomplete types of bundle branch block.

2. Ventricular tachycardias from the ventricle below the intact branch produce bundle branch block patterns from the opposite side.

3. The QRS morphology of ventricular tachycardias from the ventricle below the affected bundle branch depends upon the time of the cardiac cycle in which the stimuli occur. Between the T wave and the beginning of P, complete bundle branch block patterns are produced. Stimuli which fall into the P-R interval fuse with the activation wave coming from the auricle through the unaffected branch and result in narrowed or relatively normal

QRS complexes. Fusion beats can be seen which exhibit the typical morphology of the WPW syndrome if the ventricular stimulus is discharged immediately after the P wave.

References

1. Robinson, G. C. and Herrmann, G. R. Paroxysmal tachycardia of ventricular origin and its relation to coronary occlusion. *Heart*, 8: 59, 1921.
2. Herrmann, G. R. and Hejtmancik, M. R. A clinical and electrocardiographic study of paroxysmal ventricular tachycardia and its management. *Ann. Int. Med.*, 28: 989, 1948.
3. Armbrust, C. A. and Levine, S. A., Paroxysmal ventricular tachycardia: a study of 107 cases. *Circulation*, 1: 28, 1950.
4. Bellet, S. Clinical Disorders of the Heart Beat, p. 118, 208. Philadelphia, 1953. Lea and Febiger.
5. Hewlett, A. W. A case showing bundle branch block with extrasystoles originating in the ventricular septum. *Heart*, 9: 1, 1927.
6. Wilson, F. N. and Herrmann, G. R. Bundle branch block and arborization block. *Arch. Int. Med.*, 26: 153, 1920.
7. Scherf, D. and Kisch, B. Ventricular tachycardias with variform ventricular complexes. *Bull. New York M. Coll.*, 2: 73, 1939.
8. Scherf, D. and Schott, A. Extrasystoles and Allied Arrhythmias, p. 30, 144. New York, 1953. Grune & Stratton.
9. Mahaim, I. Les Maladies Organiques du Fais Ceau de His-Tawara, p. 425. Paris, 1931. Masson et cie.
10. Lewis, T. Premature contractions arising in the junctional tissues. *Quart. J. Med.*, 5: 1, 1911.
11. Lewis, T. and Allen, H. W. An instance of premature beats arising in the auriculoventricular bundle of a young child. *Am. J. M. Sc.*, 145: 667, 1913.
12. Holzmann, M. Klinische Elektrokardiographie, p. 491. Stuttgart, 1955. Georg Thieme Verlag.
13. Simon, A. J. and Langendorf, R. Intraventricular block with ectopic beats approaching normal QRS duration. *Am. Heart J.*, 27: 345, 1944.
14. Bisteni, A., Sodi-Pallares, D., Medrano, G. A. and Pileggi, F. Nuevos conceptos para el diagnostico de las extrasistoles ventriculares. *Arch. Inst. cardiol. Mexico*, 27: 46, 1957.
15. Bisteni, A., Medrano, G. A. and Pileggi, F. Personal communication.
16. Bisteni, A., Sodi-Pallares, D., Medrano, G. A. and Pileggi, F. A new approach for the recognition of ventricular premature beats. *Am. J. Cardiol.*, 5: 358, 1960.
17. Scherf, D. Studies on auricular tachycardia caused by aconitine administration. *Proc. Soc. Exper. Biol. & Med.*, 64: 233, 1947.
18. Scherf, D., Morgenbesser, L. J., Nightingale, E. J. and Schaeffeler, K. T. Mechanism of ventricular fibrillation. *Cardiologia*, 16: 232 1950.
19. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W. and Kruger, H. E. The Auricular Arrhythmias, p. 350. Springfield, Ill., 1952. Charles C Thomas.
20. Sodi-Pallares, D., Thomsen, E., Barbato, E., Soberon, A. F., Fishleder, B. L. and Estandia, A. Bloqueos incompletos de rama. *Arch. Inst. cardiol. México*, 18: 497, 1948.
21. Rodriguez, M. I. and Sodi-Pallares, D. The mechanism of complete and incomplete bundle branch block. *Am. Heart J.*, 44: 715, 1952.
22. Sodi-Pallares, D. and Calder, R. M. New Bases of Electrocardiography, p. 372. St. Louis, 1956. C. V. Mosby.
23. Penaloza, D. and Tranchesi, J. The three main vectors of the ventricular activation process in the normal human heart. *Am. Heart J.* 49: 51, 1955.
24. Guzman, S. V., deLeon, A. C., Jr., West, J. W. and Bellet, S. Cardiac effects of isoproterenol, norepinephrine and epinephrine in complete A-V heart block during experimental acidosis, and hyperkalemia. *Circulation Res.*, 7: 666, 1959.
25. Rodriguez, M. I., Sodi-Pallares, D. and Anselmi, A. Activation of the free ventricular wall of dog hearts. Inter-American Congress of Cardiology, Buenos Aires, 1952.
26. Rodriguez, M. I., Anselmi, A. and Sodi-Pallares, D. Activation de las paredes libres ventriculares. I. Activacion endocardia. *Arch. Inst. cardiol. México*, 23: 624, 1953.
27. Rodriguez, M. I., Sodi-Pallares, D. and Anselmi, A. Activacion de las paredes libres ventriculares. II. Activacion del espesor de las paredes libres. *Arch. Inst. cardiol. México*, 23: 756, 1953.
28. Sodi-Pallares, D., Anselmi, A. and Rodriguez, M. I. Activacion de las paredes libres ventriculares. III. Activacion epicardica. *Arch. Inst. cardiol. México*, 24: 3, 1954.
29. Sodi-Pallares, D., Rodriguez, M. I., Chait, O. and Zuckermann, R. The activation of the interventricular septum. *Am. Heart J.*, 41: 569, 1961.
30. Wilson, F. N. and Herrmann, G. R. An experimental study of incomplete bundle branch block and of the refractory period of the heart of the dog. *Heart*, 8: 229, 1921.
31. Muller, O. F., Lewis, D., Deitz, G. and Bellet, S. Unpublished observations.

Report on Therapy

The Use of Vasopressors in Cardiac Arrhythmias, Particularly Ventricular Tachycardia*

WALDO GREENSPAN, M.D. *and* ZARIE L. SHAHGALDIAN, M.D.

Hackensack, New Jersey

IN THE PAST several years there has been much comment in the literature dealing with the effect of vasopressors on cardiac arrhythmias.[1-8] The effect of such arrhythmias in producing hypotension has been long recognized. In Wolff's series,[9] 56 per cent of the patients demonstrated hypotension in the presence of arrhythmias. In ventricular tachycardia not only hypotension but also severe impairment of coronary blood flow can occur even at slow rates. It has been demonstrated previously[6] that raising the blood pressure 30 mm. Hg can augment coronary blood flow by 30 per cent. It is, therefore, imperative to relieve shock secondary to an arrhythmia such as ventricular tachycardia as soon as possible, especially in situations where the occurrence of myocardial infarction has further compromised the nutrition of the heart. On the other hand, caution in the use of vasopressor agents is necessary because overenthusiastic use may lead to serious complications due to myocardial toxicity.[5,10-15]

It is the purpose of this paper to present reports of four cases of ventricular tachycardia; three reverted to normal rhythm after administration of vasopressor drugs. The fourth case was precipitated by such therapy.

CASE REPORTS

CASE 1. A thirty-four year old white man was admitted to the hospital with frequent episodes of syncope. One year previously he had had a myocardial infarction. In the interim he had noted recurrent palpitations with syncope although his physician had never seen him in such an attack.

Physical examination revealed an apprehensive man with a regular apical rate of 160 per minute and blood pressure of 120/80 mm. Hg. An electrocardiogram revealed a supraventricular tachycardia, rate 160 per minute, which did not respond to intravenous administration of phenylephrine but reverted promptly to normal rhythm following digitalization. An electrocardiogram after reversion (Fig. 1A) revealed an old anterior wall infarction and persistent S-T segment elevation in leads V_3-V_6.

The patient was well until eight days later when he suddenly noted numbness of the arms and marked palpitations. An electrocardiogram at this time (Fig. 1B) revealed a ventricular tachycardia probably arising from the apical region with a rate of 150 per minute. Over the next thirty-six hours the tachycardia persisted despite the oral administration of procaine amide and later, quinidine sulfate. There was no evidence of shock. At the end of thirty-six hours, quinidine was given intravenously (0.56 gm. in 150 cc. dextrose and water); five minutes later the blood pressure was not obtainable although tachycardia persisted. Intravenous administration of metaraminol was started (300 mg. in 500 cc. of 5 per cent dextrose in water) and one minute later the blood pressure was 120/80 with reversion to normal sinus rhythm (Fig. 1C). The patient was given a maintenance dose of oral quinidine and metaraminol was discontinued. He was subsequently discharged without further incident. The diagnosis was ventricular aneurysm, later proved at surgery.

Comment: Ventricular tachycardia developed on the eighth day of hospitalization in a patient with a ventricular aneurysm due to

* From the Hackensack Hospital, Hackensack, New Jersey.

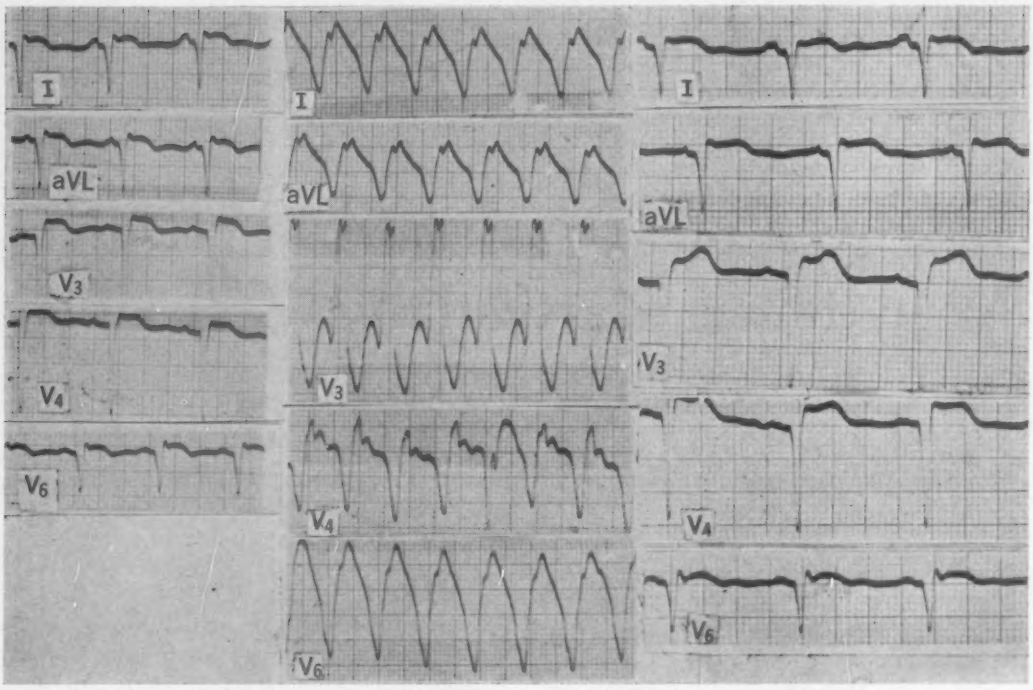


FIG. 1. Case 1. A, obtained August 27, 1958, prior to onset of ventricular tachycardia. B, obtained September 2, 1958; ventricular tachycardia, rate 150 per minute. C, taken September 4, 1958, shows conversion to normal sinus rhythm after administration of metaraminol. Persistent S-T elevation indicates the presence of a ventricular aneurysm. In A and C, leads V_3, V_4 and V_6 were recorded at half standardization.

old myocardial infarction. There was no evidence of a recent infarction. The tachycardia, although lasting thirty-six hours, did not cause hypotension because it was the so-called "benign ventricular tachycardia" arising from the apex of the heart. Tachycardia was not affected by the oral administration of procaine amide or quinidine. With the onset of shock which followed the intravenous administration of quinidine, there was prompt response of both the blood pressure and tachycardia one minute after the administration of intravenous metaraminol.

CASE 2. A sixty-one year old white man entered the hospital because of severe retrosternal pain of two hours' duration. He had been treated one and a half years previous for a myocardial infarction and since that time had been taking digitalis and was asymptomatic. On examination the pulse was 80 per minute and regular; the blood pressure was 142/90 mm. Hg. An electrocardiogram on admission (Fig. 2A) revealed normal sinus rhythm, prolonged P-R interval and marked S-T elevation in leads II, III and aVF, indicative of recent inferior wall infarction.

Two days later the patient suddenly went into shock with a blood pressure of 90/50. Intravenous metaraminol (200 mg. in 500 cc. 5 per cent dextrose in water) was administered with a prompt rise in blood pressure to 120/80. An electrocardiogram revealed sinus tachycardia, rate 120 per minute, with first degree heart block. Metaraminol was discontinued and the blood pressure remained stable. The electrocardiogram showed an evolutionary pattern of recent inferior wall infarction.

On the fourteenth hospital day, a tachycardia of 200 per minute developed and the patient again went into shock with a blood pressure of 80/60. An electrocardiogram at this time (Fig. 2B) suggested a ventricular tachycardia which was confirmed by esophageal leads. The rate was 180 per minute. He was given oral quinidine and then procaine amide, without effect. Metaraminol was given by intravenous infusion (200 mg. in 500 cc. of 5 per cent dextrose and water), with reversion of the tachycardia to the previous rhythm after approximately 50 cc. of the solution had been administered (Fig. 2C). He was given a maintenance dose of oral quinidine and metaraminol was discontinued. He was subsequently discharged without further incident.

Comment: Ventricular tachycardia developed in a patient with a recent myocardial infarction and did not respond to either procaine amide or quinidine orally, but did respond promptly to metaraminol by intravenous infusion. This case would support the idea that the initial treatment of choice in such situations would be a vasopressor agent.

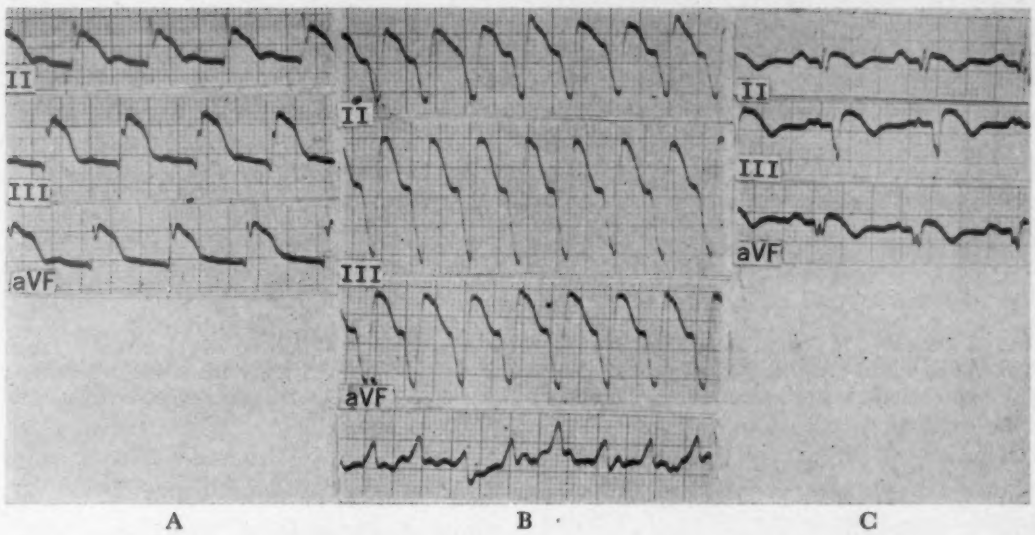


FIG. 2. Case 2. A, taken July 13, 1959, showing normal sinus rhythm, first degree atrioventricular block and acute inferior wall infarction. B, July 29, 1959, showing ventricular tachycardia. Note independent P waves in the esophageal lead (20 cm. level), confirming the diagnosis. C, obtained July 29, 1959, showing conversion to normal sinus rhythm after therapy with metaraminol.

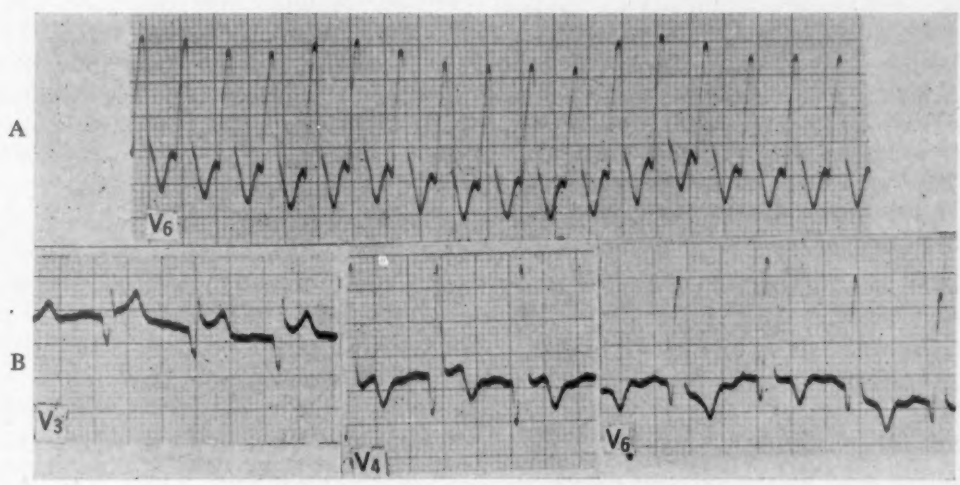


FIG. 3. A, lead V_6 demonstrates ventricular tachycardia, rate 240 per minute. B, normal sinus rhythm after therapy with metaraminol. The deep Q waves and S-T elevation in V_3 and V_4 indicate acute anteroseptal myocardial infarction.

CASE 3. A seventy-two year old white man was admitted to the emergency room in shock. He was dyspneic, cold and cyanotic, but conscious. The blood pressure and pulse were unobtainable. An electrocardiogram revealed ventricular tachycardia, rate 160 per minute (Fig. 3A). Immediate vasopressor therapy was administered (300 mg. of metaraminol in 500 cc. of 5 per cent dextrose in water intravenously). Within five minutes the electrocardiogram revealed reversion of ventricular tachycardia to normal sinus rhythm, rate 86 per minute. There was evidence of an acute myocardial infarction involving the anteroseptal region (Fig. 3B). Although there was significant clinical improvement, the blood pressure remained unobtainable until infusion of norepinephrine was started. The blood pressure was well maintained subsequently.

Comment: Metaraminol therapy terminated an attack of ventricular tachycardia despite continued hypotension. This would imply a direct action on the myocardium rather than a secondary effect relating to an elevation of systemic blood pressure.

CASE 4. A thirty-eight year old white man was admitted to the hospital with precordial pain of three days' duration. On admission the blood pressure was 102/70 mm. Hg and the pulse was 72 per minute and regular. Physical examination was within

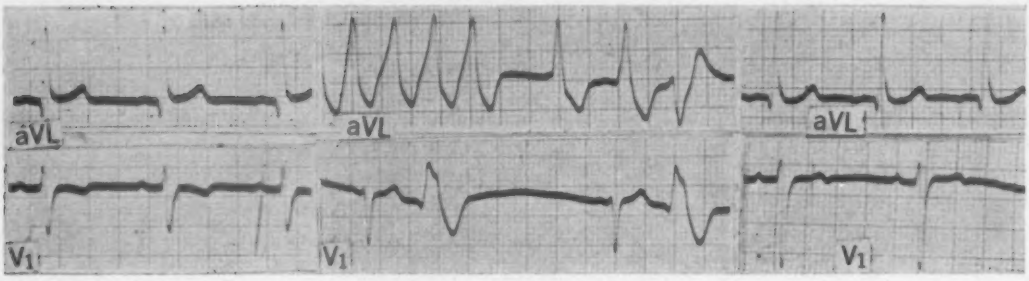


FIG. 4. Case 4. A, taken December 2, 1957. Admission record within normal limits. B, taken December 4, 1957, showing short runs of ventricular tachycardia and bigeminal rhythm following intramuscular doses of metaraminol. C, taken December 4, 1957, showing reversion to normal sinus rhythm.

normal limits. An admission electrocardiogram was not remarkable (Fig. 4A).

Two days later the patient had severe pain in the chest with radiation to both arms, necessitating administration of morphine sulfate. The blood pressure dropped to 78/50 mm. Hg; he was cold, clammy and cyanotic. He was given 30 mg. metaraminol intramuscularly. Within fifteen minutes his blood pressure was 190/110, he felt hot, flushed and complained of palpitation. An electrocardiogram at this time revealed short runs of ventricular tachycardia (Fig. 4B). One minute later bigeminal rhythm was present, finally reverting to normal sinus rhythm a few minutes later (Fig. 4C). Serial electrocardiograms over the next three weeks showed no evolutionary pattern of myocardial infarction.

Comment: The use of metaraminol to raise this patient's blood pressure first caused runs of ventricular tachycardia, later bigeminal rhythm, fortunately reverting to normal sinus rhythm without further treatment. Better control of dosage would have been obtained by using intravenous infusion of the vasopressor agent.

COMMENTS

It has been demonstrated by many workers[5,9,16] that any disturbance of cardiac rhythm may influence systemic blood pressure, which in itself is essential to coronary blood flow and the proper nutrition of myocardium. The severity of these effects on coronary flow depends on the site of origin, type, rate and duration of the arrhythmia and the degree of myocardial disease.

Site of Origin, Type and Rate of Arrhythmia: Tachycardia in general and tachyarrhythmias of atrial origin have a better prognosis and fewer side effects than those arising from the atrioventricular node or ventricles. Experiments[5,6] in dogs have revealed that the degree of drop in systemic blood pressure with atrial premature contractions is only about 5 per cent. In sinus tachycardia or paroxysmal atrial tachycardia, provided ventricular rates do not exceed 180 to 190 per minute, there may be no significant change in systemic blood pressure. On the contrary, there is usually an increase in cardiac output and coronary blood flow. However, when the rate exceeds 180 to 190 per minute a marked drop in systemic blood pressure of as much as 35 per cent may occur. In atrial fibrillation the fall of the blood pressure depends on the ventricular rate, which determines the time of diastolic filling. Thus, during slow atrial fibrillation systemic blood pressure may not be altered. On the other hand, atrial fibrillation with a rapid ventricular rate of 120 or above can cause a 40 per cent drop in systemic blood pressure. In atrial flutter, effects on blood pressure are not as significant as in atrial fibrillation. The greater the degree of block and the slower the ventricular rate the less the drop in blood pressure.[5]

Ventricular premature contractions may or may not cause impairment of cardiac output although up to a 13 per cent drop in systemic blood pressure has been reported.[7] This is noted more often in cases of bigeminy. Ventricular tachycardia is always considered a medical emergency and a decrease of between 60 to 90 per cent in coronary blood flow and systemic blood pressure has been reported. This becomes more manifest when the site of origin of the ectopic beat is taken into consideration. An ectopic beat originating in the apex of the heart is less dangerous than one arising at the base, which would interfere with proper filling and produce the so-called "malignant ventricular tachycardia."[5] Ventricular fibrillation is usually a terminal event, for there is no filling, no cardiac output, systemic blood

pressure is zero and there is no coronary circulation.

The hemodynamics of the coronary circulation are impaired during tachyarrhythmias. With tachycardia the work of the heart is increased resulting in increased nutritional requirements. On the other hand, the arrhythmia itself causes impaired ventricular filling and output with a fall in systemic blood pressure and, therefore, in coronary perfusion pressure. This results in myocardial ischemia and impaired myocardial contraction with a further drop in systemic blood pressure and perpetuation of the arrhythmia.

Degree of Myocardial Disease and Duration of the Arrhythmia: Tachycardia in the presence of coronary sclerosis is a hazardous factor. It is not uncommon for young patients to have episodes of paroxysmal atrial tachycardia at a rapid rate lasting for several days without evidences of discomfort or circulatory disturbance, whereas such a tachycardia in an older patient may cause myocardial infarction or pulmonary edema in only a few hours, depending on the state of the coronary arteries. Any arrhythmia in a heart with sclerotic vessels will greatly increase the degree of ischemia which may lead to more severe myocardial hypoxia and even true infarction. Thus, a simple arrhythmia such as premature contractions may cause ischemia with or without angina; or on the other hand, myocardial ischemia itself may cause extrasystoles.[17,18] Improvement of ischemia by an elevation of the systemic blood pressure will often abolish extrasystoles and anginal pain.

It is generally agreed that the extent of damage following myocardial infarction depends on the amount of the blood flow provided by the collateral circulation. In the presence of coronary sclerosis, although collaterals are present, the effective total blood flow is diminished. This may be further reduced in the presence of an arrhythmia.[5,7] Since a difference of only a few milliliters of blood can markedly increase myocardial oxygenation, this can be achieved by the rapid reversion of the arrhythmia, and further necrosis prevented.

Action of Vasopressor Agents in Terminating Cardiac Arrhythmias: It is accepted that coronary blood flow is a function of the systemic blood pressure or, more directly, of the aortic perfusion pressure.[5,19] Although other factors such as exercise, digestion, metabolic needs and reflex action of cardiac nerves[19,20] influence coronary blood flow, systemic blood pressure seems to be one of the most important. The maintenance of this pressure during an arrhythmia, especially when associated with coronary artery disease, becomes vital. Even if vasopressor agents do not terminate the arrhythmia, by maintaining a proper systemic blood pressure and therefore adequate coronary artery flow, sufficient time will be provided for the other antiarrhythmic agents to act. The hypertensive action of the catecholamines seems to affect arrhythmias even when the heart is completely denervated, indicating that their site of action may be directly on the myocardium or the conductive system.

Vasopressors, by acting on vascular beds, increase peripheral vascular resistance, thus raising systemic blood pressure. Norepinephrine and metaraminol are also coronary vasodilators and act directly on the coronary arteries, although their effects are not always uniform.[21] Wegria and his co-workers[22] believe that vasopressors increase myocardial metabolism, releasing metabolites which have vasodilator properties. On the other hand, Wiggers and others[23–25] believe that after the use of vasopressors a transient increase in coronary artery resistance takes place which persists until cardiac metabolites are released with secondary coronary vasodilatation. Although the intermediate steps are indefinite the end result of vasopressor action seems to be a coronary vasodilatation with increased oxygenation of the myocardium.[25]

Following the administration of vasopressors transient changes such as S-T elevation followed by inversion and coving of T waves have been reported in the electrocardiogram, simulating an early coronary occlusion.[26] In addition, recent experiments on dogs[14,15] have demonstrated that overdosage of vasopressor agents may lead to myocarditis with fatty changes and hemorrhagic necrosis of the myocardium. Major arrhythmias may also be precipitated directly due to overdosage, such as frequent ventricular premature contractions, bigeminy, bidirectional tachycardias and ventricular tachycardia (Case 4).[5,14] The cause of these events has not yet definitely been determined. It has been postulated that the catecholamines increase the rate of myocardial oxygen consumption, causing a relative hypoxia often resulting in a cardiac arrhythmia.[27] In addition, vasopressors act on the transmembrane potential of the cardiac cell, causing a shift of potassium ion into the extracellular compartment, so that hypokalemia would favor production of an ar-

rhythmia.[28] There seems to be a critical level of the systolic blood pressure between 180–190 mm., at which most of the arrhythmias become manifest, as well as a critical level of catecholamines in the serum.[14] To avoid this, the pressor agent should be given by intravenous infusion for better control of dosage rather than by intramuscular administration. It should be remembered that sodium ion antagonizes the effect of potassium ion on the myocardium[29] and, therefore, should not be used as a diluent during vasopressor therapy.

The concept of terminating arrhythmias by vasopressor therapy when there is a drop in systemic blood pressure is already an accepted procedure in most medical centers and by means of this therapy the mortality caused by arrhythmias and shock secondary to myocardial infarction has dropped considerably.[9,30,31]

Summary

The action of a vasopressor drug (metaraminol) in three cases of ventricular tachycardia has been demonstrated. The results suggest that the use of vasopressors to terminate ventricular tachycardias in the presence of shock is an effective method of therapy.

Vasopressors will, in most cases, terminate arrhythmias produced by shock or shock induced by arrhythmias. Even if the arrhythmia is not terminated the alleviation of the shock will sustain the patient so that further antiarrhythmic measures will have time to be effective.

In a fourth case, metaraminol given intramuscularly precipitated ventricular tachycardia. There is a critical level of systolic blood pressure (180-190 mm. Hg) above which cardiac arrhythmias may ensue during vasopressor therapy in shock. To this end, the vasopressor agents should be given by intravenous infusion for better control of dosage.

References

1. Bernstein, H. The treatment of paroxysmal supraventricular tachycardia with neosynephrin. *J. Michigan Med. Soc.*, 50: 297, 1951.
2. Schumacher, E. E., Jr. and Schmock, C. L. Control of certain cardiac arrhythmias with isopropylnorepinephrine. *Am. Heart J.*, 48: 933, 1954.
3. Donegan, C. K. and Townsend, C. V. Phenylnephrine hydrochloride in paroxysmal supraventricular tachycardia. *J.A.M.A.*, 157: 716, 1955.
4. McGinn, J. T. and Schuger, J. Levarterenol bitartrate in the treatment of cardiac arrhythmias. *Am. Heart J.*, 50: 625, 1955.
5. Corday, E., Williams, J. H., Gold, H. and DeVera, L. B. Hemodynamics of the coronary circulation during cardiac arrhythmias. *Mod. Concepts Cardiovas. Dis.*, 27: 493, 1958.
6. Corday, E. and Williams, J. H. Effect of systemic blood pressure and vasopressor drugs on coronary blood flow and the electrocardiogram. *Am. J. Cardiol.*, 3: 626, 1959.
7. Gold, H. and Corday, E. Vasopressor therapy in the cardiac arrhythmias. *New England J. Med.*, 260: 1151, 1959.
8. Bellet, S. Drug therapy in cardiac arrhythmias. *New England J. Med.*, 262: 769, 1960.
9. Wolff, L. The cardinal manifestation of paroxysmal tachycardia. *New England J. Med.*, 232: 527, 1945.
10. Tainter, M. L. and Lands, A. M. Certain actions of sympathomimetic amines on the heart. *New York J. Med.*, 53: 1433, 1953.
11. Sector, W. E., McLaughlin, J. T. and Dowling, C. Ventricular arrhythmia induced by methoxamine hydrochloride. *J.A.M.A.*, 158: 1025, 1955.
12. Hoffman, B. F., Siebens, A. A., Cranfield, P. F. and Brook, C. M. Effect of epinephrine and norepinephrine on ventricular vulnerability. *Circulation Res.*, 3: 140, 1957.
13. Littler, T. R. and McKendrick, C. S. L. Noradrenalin in myocardial infarction. *Lancet*, 2: 825, 1957.
14. Szakacs, J. D. and Mehlman, M. S. Pathological changes induced by *l*-norepinephrine. *Am. J. Cardiol.*, 5: 619, 1960.
15. Maling, H. M., Highman, B. and Thompson, E. C. Some similar effects after large doses of catecholamines and myocardial infarctions in dogs. *Am. J. Cardiol.*, 5: 628, 1960.
16. Corday, E., Gold, H., DeVera, L. B., Williams, J. H. and Fields, J. The effect of cardiac arrhythmias on the coronary and systemic circulation. *Ann. Int. Med.*, 50: 535, 1959.
17. Katz, L. N. and Pick, A. Clinical Electrocardiography. 1. Arrhythmias, p. 169. Philadelphia, 1956. Lea & Febiger.
18. Levine, H. D., Lown B. and Streeper, R. B. Clinical significance of post extrasystolic T wave changes. *Circulation*, 6: 538, 1952.
19. Gregg, D. E. Coronary Circulation in Health and Disease, p. 104. Philadelphia, 1950. Lea & Febiger.
20. Essex, H. E., Herrick, J. F., Baldes, E. J. and Mann, F. C. Blood flow in circumflex branch of left coronary artery of the intact dog. *Am. J. Physiol.*, 117: 271, 1936.
21. Leusen, I. and Essex, H. E. Effects of epinephrine norepinephrine and khellin on circulation thru isolated prepared heart. *Am. J. Physiol.*, 172:226, 1953.
22. Wegria, R. Pharmacology of the coronary circulation. *Pharmacol. Rev.*, 3:197, 1951.
23. Wiggers, C. J. The interplay of coronary vascular resistance and myocardial compression in regulating coronary flow. *Circulation Res.*, 2: 271, 1954.
24. Beine, R. M. Effect of epinephrine and norepinephrine on coronary circulation. *Circulation Res.*, 6: 644, 1958
25. Denison, A B. and Green, H. D. Effects of autonomic nerves and their mediators on the coronary

circulation and myocardial contraction. *Circulation Res.*, 6: 633, 1958.

26. FRIEDBERG, C. K. Diseases of the Heart, 2nd edition, p. 335. Philadelphia, 1956. W. B. Saunders.
27. RAAB, W. Neurohumoral factors in the origin and treatment of angina pectoris. *Ann. New York Acad. Sc.*, 64: 528, 1956.
28. MELVILLE, K. I. and KOROL, B. Cardiac drug responses and potassium shifts (section 1). *Am. J. Cardiol.*, 2: 81, 1958.
29. GRUMBACH, L. Difibrillatory effects of low sodium solutions on ventricular fibrillation in isolated hearts of rabbits. *Circulation Res.*, 5: 362, 1957.
30. GRIFFITH, G. C., WALLACE, W. B., COCHRAN, B., JR., NEILICH W. E. and FRASHER, W. G. The treatment of shock associated with myocardial infarction. *Circulation*, 9: 527, 1954.
31. SAMPSON, J. J. and ZIPSER, A. Norepinephrine in shock following myocardial infarction. *Circulation*, 9: 38, 1954.

Review

Idiopathic Myocardial Hypertrophy*

MARVIN A. SACKNER, M.D., DAVID H. LEWIS, M.D.,† MORTON J. ROBINSON, M.D. *and* SAMUEL BELLET, M.D., F.A.C.C.

Philadelphia, Pennsylvania

THE term "idiopathic myocardial hypertrophy" has been applied to the clinical picture of cardiomegaly of unknown cause which occurs in relatively young adults in whom a severe grade of congestive heart failure is a dominant feature.[1–3] Such diseases as hypertension, rheumatic fever, disease of the coronary artery, myocarditis, thyrotoxicosis, syphilis, beriberi, congenital malformations, fibroelastosis, collagen diseases, granulomatous diseases, amyloidosis and hemochromatosis are necessarily excluded as causes of this hypertrophy. Most of these diseases can be ruled out by simple clinical and laboratory means but others offer difficult problems in differential diagnosis. Based upon a review of twenty-one cases observed at this hospital over a five year period, this discussion will deal with the clinical features and differential diagnosis of this condition.

MATERIALS AND METHODS

The records of twenty-one adults with idiopathic myocardial hypertrophy hospitalized during the period from January, 1954 through December, 1959 were reviewed. The specific causes of cardiomegaly as previously mentioned were excluded by clinical and laboratory methods and examinations through necropsy obtained in eleven instances (52 per cent).

These patients were divided into three groups based on the clinical course. *Group 1* included those patients with severe congestive heart failure who responded poorly to the usual therapeutic measures (twelve cases). The symptoms of the patients in this group correspond to those which are usually described as characteristic of "idiopathic myocardial hypertrophy." *Group 2* consisted of patients with cardiac enlargement and minimal to moderate signs of congestive heart failure (six cases). This group has not usually been classified as "idiopathic myocardial hypertrophy." *Group 3* included patients with portal cirrhosis who had mild cardiac disability (three cases).

Data were treated by the Chi square test with Yater's correction factor when appropriate.[4]

RESULTS

Incidence: Idiopathic myocardial hypertrophy was recorded in 0.009 per cent of admissions to the medical service of the Philadelphia General Hospital during the period of this study. This condition was found in 0.2 per cent of 4,000 consecutive necropsies of adults, and was observed in 1 per cent of hearts weighing 500 gm. or over from patients dying of all causes. It is noteworthy that during the five year course of this study, not one necropsy revealed fibroelastosis in an adult.

Age, Sex and Race (Table I): The average age of the members of the entire group was thirty-nine years, with a range of twenty-eight to fifty-seven years. The ages of those for each group were fairly comparable. In Group 1 (idiopathic myocardial hypertrophy with severe congestive heart failure) the ages were 40 ± 7 years; in Group 2 (idiopathic myocardial hypertrophy with minimal cardiac symptoms) the ages were 37 ± 8 years; in Group 3 (idiopathic myocardial hypertrophy and portal cirrhosis) the ages were 44 ± 2 years. Eleven of the twelve patients in Group 1, 3 of 6 in Group 2 and 3 of 4 in Group 3 were men. The high incidence of the disease in Negroes probably reflects the population of the Phila-

* From the Division of Cardiology and Pathology, Philadelphia General Hospital, Philadelphia, Pennsylvania. This work was supported by a grant in aid from the American Heart Association, by a research grant (H-2559) from the National Heart Institute of the National Institutes of Health, and by a contract (NR 102-470) with the Offices of Naval Research, Department of the Navy.

† Established Investigator of the American Heart Association.

TABLE I

Summary of Twenty-one Cases of Idiopathic Myocardial Hypertrophy

Case No.	Age and Sex	Race	Duration from Onset of Symptoms (mo.)	Result	Autopsy
			Group 1		
1	33, M	W	6	Dead	Yes
2	39, M	N	22	Dead	Yes
3	44, M	N	11	Dead	Yes
4	57, M	N	60	Dead	Yes
5	28, M	N	4	Dead	Yes
6	39, F	N	18	Dead	Yes
7	30, M	N	6	Dead	Yes
8	34, M	N	16	Dead	No
9	39, M	N	54	Living	...
10	45, M	W	12+	*	...
11	37, M	N	17	Living	...
12	53, M	N	3	Living	...
			Group 2		
13	28, M	N	8	Dead	Yes
14	34, M	N	18	Dead	Yes
15	44, M	N	18+	*	No
16	37, F	N	42	Living	...
17	47, F	N	115	Living	...
18	29, F	N	12	Living	...
			Group 3		
19	44, M	W	29	Dead	Yes
20	41, M	W	12	Dead	Yes
21	46, F	N	55	Living	No

* Lost to follow-up.

TABLE II

Clinical Features

Features	Group 1 (12)	Group 2 (6)	Group 3 (3)	Total No.	Total %
Dyspnea	12	5	2	19	90
Rales	12	5	2	19	90
Hepatomegaly	11	2	3	16	76
Increased jugular venous distention	12	1	2	15	71
Peripheral edema	9	3	3	15	71
Chest pain	6	2	1	9	43
Hemoptysis	6	2	0	8	38
Pleural effusion	5	2	1	8	38
Pulmonary embolism	4	2	1	7	33
Alcoholism	3	1	3	7	33
Antecedent upper respiratory infection	3	2	1	6	29
Systemic emboli	3	2	0	5	24
Ascites	4	0	1	5	24
Digitalis toxicity	3	1	0	4	19
Myocardial infarction	0	1	0	1	5

delphia General Hospital rather than a racial predisposition. Four patients in Group 1, one in Group 2 and one in Group 3 died within one year following the onset of symptoms.

Clinical Features (Table II): In the patients of all groups the most common presenting symptom was dyspnea, which varied in duration from a few days to several years. Peripheral edema occurred more frequently and was of greater severity in the patients in Groups 1 and 3 than in those of Group 2. Hemoptysis was recorded in 38 per cent of the patients and was mild. A history of alcoholism was obtained from one third of the patients, including all the cirrhotic subjects. Pain in the chest when present was nonspecific and fleeting in character. In Case 14, angina-like pain was associated with a subendocardial infarction. This patient showed asymptomatic cardiomegaly for nineteen years preceding this event. Two other patients (Cases 13 and 18) also had cardiomegaly of long duration, documented eight years prior to their first symptoms. Infections of the upper respiratory tract preceded the onset of symptoms by a few weeks to a few months in 29 per cent of patients.

Physical examination generally revealed well nourished subjects. The lungs often showed fine basilar rales. Signs of peripheral congestion, i.e., tender, enlarged liver, jugular venous distention, peripheral edema and ascites, were more marked in Group 1 than in Group 2. In Group 3 it was difficult to differentiate a cardiac from a hepatic basis in interpreting these signs. Pulmonary emboli were diagnosed clinically in 33 per cent of the patients and systemic emboli in 24 per cent.

The auscultatory findings are summarized in Table III. Gallop rhythms, usually protodiastolic (confirmed by phonocardiograms), were observed in 52 per cent of the patients. These were not observed in the cirrhotic patients. Functional apical systolic murmurs were heard in three patients. In Case 6 a moderately loud tricuspid systolic murmur was found, by intracardiac phonocardiography, to result from tricuspid regurgitation. This was apparently

TABLE III
Auscultatory Findings

Findings	Group 1	Group 2	Group 3	Total No.	Total %
Gallop sounds	8	3	0	11	52
Protodiastolic	5	2	0	7	
Presystolic	2	0	0	2	
Summation	1	1	0	2	
Murmurs	4	0	1	5	24
Functional apical systolic	3	0	0	3	
Functional tricuspid systolic	1	0	0	1	
Functional basal systolic	0	0	1	0	
Systolic clicks	1	0	0	1	5

TABLE IV
Electrocardiographic Findings

Findings	Group 1	Group 2	Group 3	Total No.	Total %
Rhythm					
Sinus	11	6	2	19	100
Arrhythmias with digitalis	3	1	0	4	21
Ventricular tachycardia	0	1	0	1	5
Biphasic P wave in V_1	11	3	2	16	84
QRS					
Delayed intrinsicoid deflection V_6	4	3	0	7	37
Left bundle branch block	1	1	1	3	16
Right bundle branch block	1	0	0	1	5
T wave					
Inverted or flat in I, aVL and lateral precordial leads	9	4	0	13	81*
Subendocardial infarction	0	1	0	1	5
Axis					
Normal	4	4	0	8	42
Left	7	2	2	11	58
Left ventricular hypertrophy	10	4	0	14	74

*Excluding left bundle branch block.

secondary to congestive heart failure since no deformity of the valve was found at necropsy.

Heart failure in the members of Group 1 responded poorly to vigorous digitalis and diuretic therapy. On the other hand, the congestive heart failure observed in those patients with minimal symptoms (Group 2) and in cirrhotics responded promptly to the usual measures. The mode of death among these patients was usually severe peripheral vascular collapse.

Electrocardiograms: The electrocardiograms of fourteen patients showed criteria of left ventricular hypertrophy (Table IV). Inverted or flattened T waves in leads I, aVL and the lateral precordial leads were found in the majority of tracings. The electrical axis was normal in 42 per cent of the cases and devi-

TABLE V
Comparison of Electrocardiographic Findings in Cases of Cardiac Hypertrophy of All Causes

	Idiopathic Myocardial Hypertrophy		Cardiomegaly (>500 gm.) Exclusive of Infarct		Cardiomegaly (>500 gm.) Complicated by Infarct	
	No.	%	No.	%	No.	%
Total Cases	19	100	158	100	58	100
Rhythm						
Sinus	19	100	130	82.3	49	84.6
Atrial fibrillation	0	0	27	17.1	8	13.7
Complete heart block	0	0	1	0.6	1	1.7
P waves						
Biphasic in V_1	16	84.2	40	30.8	9	18.3
Conduction defect						
Left bundle branch block	3	15.8	9	5.7	4	6.9
Right bundle branch block	1	5.3	2	1.3	6	11.0

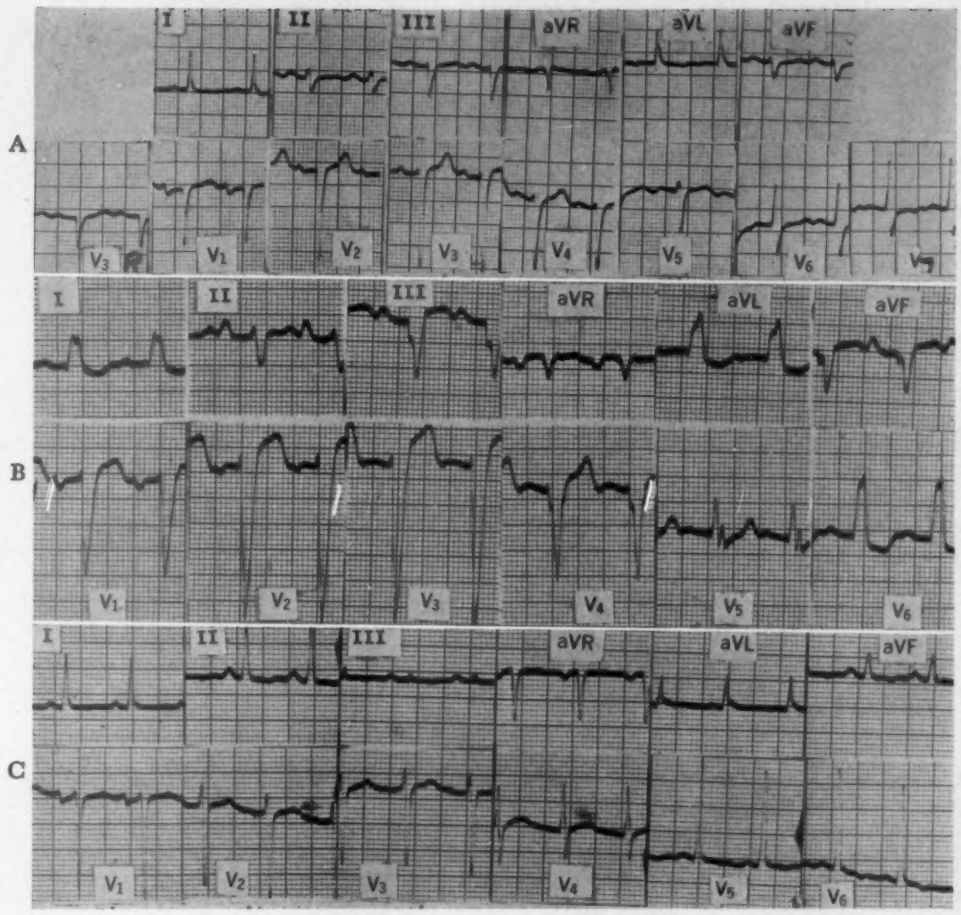


FIG. 1. Representative electrocardiograms. A, Case 6. P wave changes suggestive of left atrial disease, and nonspecific T wave changes with transition zone at V_6. B, Case 7. P wave changes suggestive of left atrial disease, first degree heart block and left bundle branch block. C, Case 13. P wave changes of left atrial disease, normal axis, delayed intrinsicoid deflection in V_6 and nonspecific T wave changes.

ated to the left in 58 per cent. A delayed intrinsicoid deflection in the left precordial leads occurred in 37 per cent of the cases and a conduction disturbance in 21 per cent. The basic rhythm in all our patients was a sinus mechanism. Ventricular extrasystoles, ventricular tachycardia and A-V dissociation occurred in four patients with digitalis toxicity. In one case ventricular tachycardia developed spontaneously.

Eighty-four per cent of the tracings showed an abnormal P wave in V_1, characterized by a brief, sharp, initial upward deflection followed by a broader, deeper, negative wave (Fig. 1). This stimulated a comparison of the electrocardiograms of patients with cardiac enlargement from all causes (Table v). Cases with hearts weighing over 500 gm. were selected from 2,000 consecutive necropsies of adults during the years of 1954 to 1956 at the Philadelphia General Hospital. Those cases with myocardial infarction were studied as a separate group. The greater incidence of a biphasic P wave in V_1 in patients with idiopathic myocardial hypertrophy compared to that in the patients in the other two groups was highly significant ($P < 0.001$). On the other hand, the greater incidence of a biphasic P wave in the group with cardiomegaly exclusive of infarction compared to the group complicated by infarction was not significant ($P = 0.2$). The broad negative deflection of the P wave expresses the delayed activation of a dilated or hypertrophied left atrium.[5] Finally, compared to the group with cardiac enlargement from other causes, the high incidence of conduction disturbances in the group with idiopathic myocardial hypertrophy was not statistically significant.

Chest Roentgenograms: Teleoroentgenograms were studied in all cases. These invariably

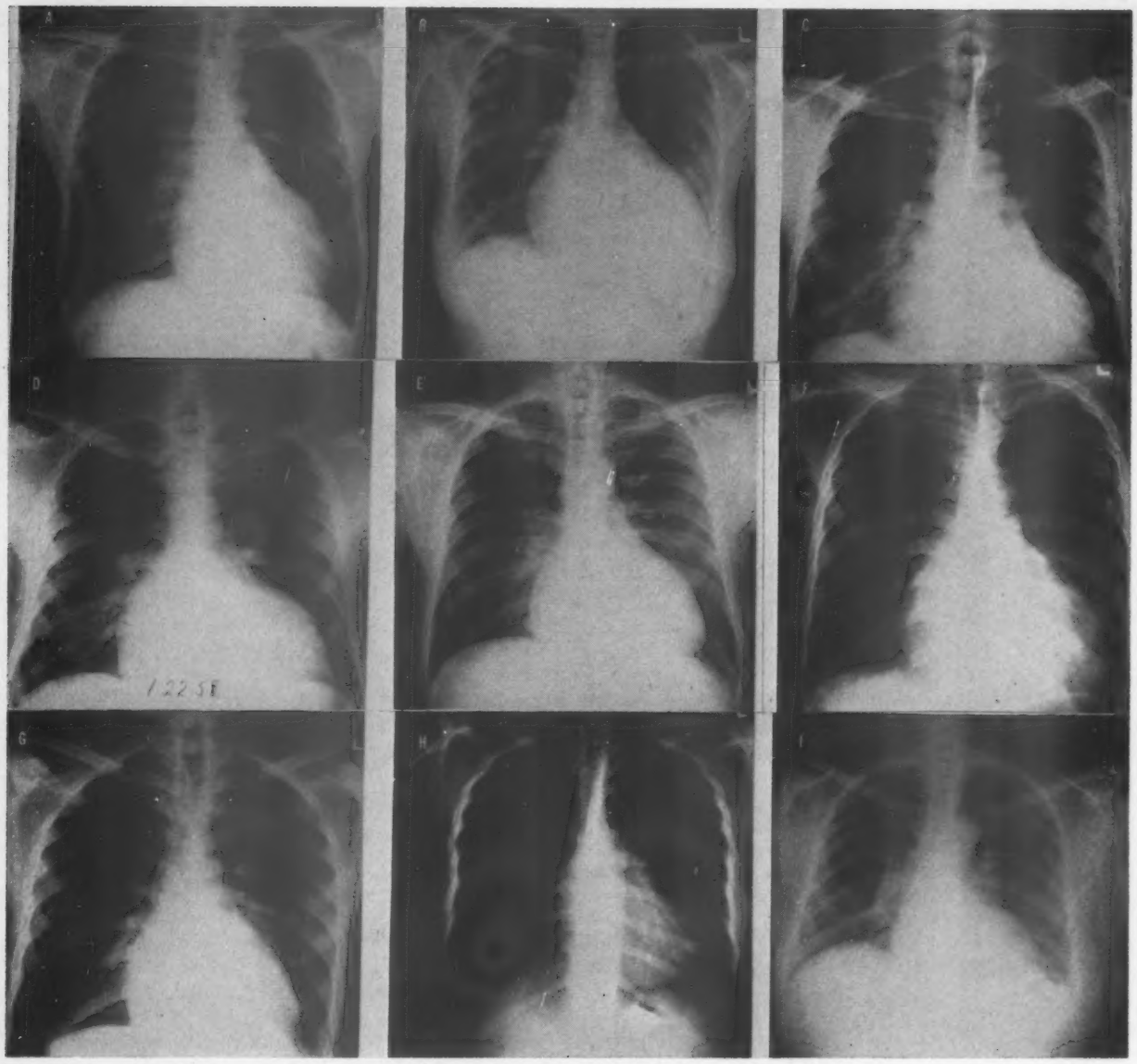


FIG. 2. Representative roentgenograms of the chest. These show nonspecific cardiac enlargement with prominent left ventricular border. A, Case 2; B, Case 6; C, Case 7; D, Case 8; E, Case 10; F, Case 11; G, Case 13; H, Case 18; I, Case 21.

showed a markedly enlarged globular heart often with a prominence of the left ventricular contour (Fig. 2). In three cases the barium-filled esophagus was displaced slightly posteriorly by an enlarged left atrium. Wedge-shaped densities in the lungs consistent with pulmonary infarction were noted in three cases.

Ballistocardiograms: The ballistocardiograms of four patients in Group 1 and of three patients in Group 2 ranged from slightly to markedly abnormal. The abnormalities consisted of prominent diastolic waves with little respiratory variation and were consistent with findings observed in congestive heart failure (Fig. 3).

Hemodynamic Data: Cardiac catheterization was carried out in five patients in Group 1 and in three patients in Group 2 (Table VI).. All except the patient in Case 18 were fully digitalized. The findings were consistent with varying degrees of congestive heart failure. The mean cardiac index was reduced to 1.95 L./min./M^2, which is 60 per cent of normal (3.25 L./min./M^2). In case 8 the cardiac output, which showed a slight reduction at rest, decreased still further with exercise. There were mild to moderate elevations of pressures of the pulmonary artery with the average being 41/21 mm. Hg. Elevations in wedge, left atrial and end diastolic pressures in the left and right ventricles were found in all subjects in whom

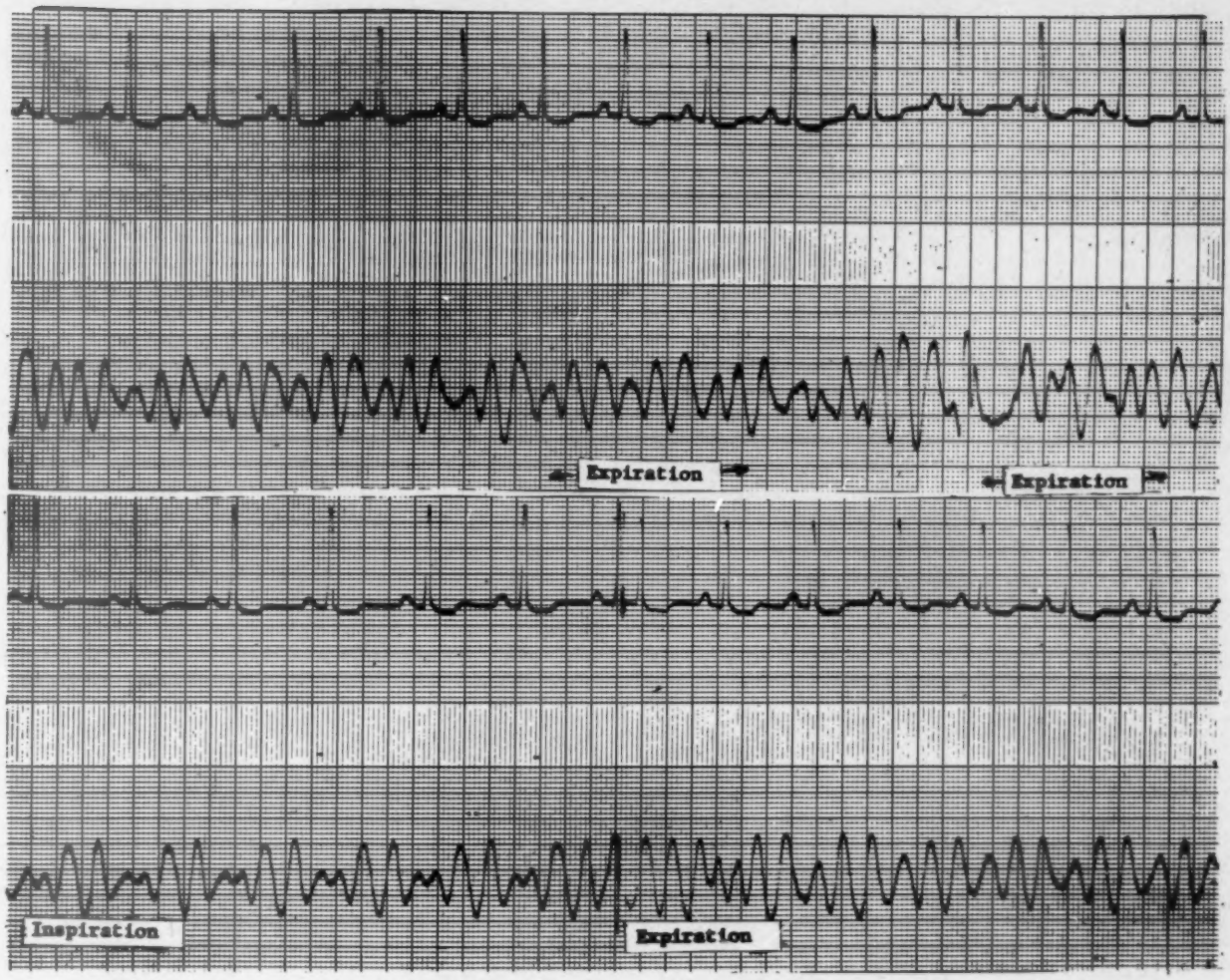


FIG. 3. Ballistocardiogram. Case 13. The diastolic waves are larger in amplitude than the systolic complex and the H wave becomes notched during held inspiration.

these pressures were determined. Arterial oxygen saturations were normal except in Case 6 in which the saturation was 86%. In Case 11 cardiac catheterizations performed seventeen months apart showed essentially no change.

Pathology: In each of the eleven cases in which autopsy was performed, the heart showed cardiac hypertrophy and dilatation of all chambers. The heart weights ranged from 500 to 960 gm., with an average of 625 gm. The pericardium was normal in all instances. The coronary arteries were patent and no occlusions in major vessels could be identified; in Case 1, slight focal intimal thickening was present and in Case 14, minimal patchy atherosclerosis. The cardiac valves were normal. The myocardium was firm and reddish. The endocardium was thin and smooth except in six cases (55 per cent); in these, underlying mural thrombi with patchy thickening were observed. Each heart had thrombi in the left ventricle; one had thrombi in the right ventricle also and another had thrombi in the right atrium. Each aorta was normal or showed minimal patchy atherosclerosis. Neither renal nor systemic vascular abnormalities suggested pre-existing hypertension. Emboli with or without infarction were distributed as follows: pulmonary, five cases; renal, four cases; splenic, two cases; mesenteric, one case.

Histologic sections of the heart showed myocardial hypertrophy. Interstitial fibrosis was focal in nine cases, generalized in one case and primarily subendocardial in one case. A small area in the right ventricle resembling an old infarction was located under a mural thrombus in Case 2, but this was considered to have played but little part in the clinical picture. In Case 14 an old posteroseptal infarction was found. However, the history of an enlarged heart nineteen years prior to the clinical and electrocardiographic manifestations of infarction

TABLE VI
Hemodynamic Data in Eight Cases of Idiopathic Myocardial Hypertrophy

Case No.	Body Surface Area (M^2)	Arterial O_2 Saturation	Arteriovenous O_2 Difference (vol. %)	Oxygen Consumption (cc./min.)	Cardiac Output (L./min.)	Cardiac Index (L./min./M^2)
6	1.55	86	6.43	159	2.47	1.59
8	2.31	95	4.83	322	6.67	2.89
	Exercise	100	7.81	488	6.25	2.70
10	1.63	99	6.60	207	3.14	1.84
11	1.57	98	8.84	182	2.06	1.31
11*	1.61	97	6.31	168	2.66	1.65
12	1.67		4.48	113	2.52	1.51
	Exercise		7.39	262	3.55	2.23
13	1.68	93	6.64	244	3.67	2.18
15	1.94	97	6.13	306	5.00	2.58
18	1.79	100	5.46	138	2.53	1.41
Mean	1.75	96	6.19	204	3.41	1.95

* Seventeen-month interval between cardiac catheterizations.

and the roentgenographic evidence of a similar degree of enlargement of the heart at the time of infarction with no change for the next eighteen months compelled us to believe that the infarction was a complication of, or incidental to, and not the cause of the cardiac enlargement.

Cultures of the heart in two cases (Cases 6 and 13) were negative for viruses.

COMMENTS

ETIOLOGIC FACTORS

Although many etiologic factors have been proposed for this disease, none has proved completely acceptable. Unfortunately, practically no histochemical or viral studies are available during the early and moderately advanced stages of this condition. Extensive pathologic studies of the end result of this disorder, myocardial hypertrophy and dilatation, were made by Elster and his associates.[1] They concluded that this condition is initiated in part by degenerative myofibrillar alteration and that successive cellular reactions lead to connective tissue proliferation. Enumeration of possible associated causal factors follows.

Congenital: Previous investigators[6–9] have reported cases of familial cardiomegaly in which symptoms were related mainly to arrhythmias rather than congestive heart failure or embolism. Slow heart rates as a result of sinus bradycardia and complete heart block were common in this group.

In our pediatric cardiology clinic, four asymptomatic Negro boys, three to eight years of age, who show cardiomegaly, normal electrocardiograms and normal cardiac catheterization data,[10] are currently being followed. Whether or not these cases represent the forerunners of idiopathic myocardial hypertrophy as observed in adults requires further study.

Hypertension: "Burnt out" hypertension does not appear to be the cause of this condition as judged by the negative history, normal funduscopic examination and absence of nephrosclerosis in these patients.

Myocarditis: The frequent occurrence of widespread patchy fibrosis in these hearts in the absence of coronary arteriosclerosis has largely influenced those favoring the theory that idiopathic myocardial hypertrophy is a residuum of myocarditis. It is difficult to exclude old inflammatory changes though these patches of fibrosis can also be explained on the basis of Thebesian vein thrombosis following intraventricular stasis during decompensation.[1,3] Mild upper respiratory infections frequently precede the onset of symptoms and there is speculation that an associated viral myocarditis is present. However, to our knowledge, no viral agent has been identified from myocardial cultures. Myocarditis secondary to a collagen disease has been fairly well excluded because of the lack of systemic involvement. Indeed, collagenous degeneration, if it occurs, is primarily subendocardial and is probably most frequently the sequela of anoxia.[1]

Nutritional Disease: Vitamin deficiencies have

TABLE VI (*cont.*)

Pressures (mm. Hg)								
RA (M)	RV (S/D)	PA (S/D)	PA (M)	PC (M)	LA (M)	LV	BA (S/D)	BA (M)
11	55/6	55/27	34	25	22	...	110/78	
8	47/8	41/26	35	21	21	?/22		
3	34/4	33/12	21	15	15	105/15	105/55	77
7	42/5	42/20	29	16	...	...	92/62	80
6	56/9	56/30	35	21	21	98/19	110/68	
...	34/4	34/17	21	15	...	...	130/82	96
...	...	...	...	...	...	...	138/72	
11	51/12	51/30	40	...	...	...	110/76	94
11	21/9	24/14	16	14	...	...	125/83	93
5	29/8	29/10	18	11	...	...	160/86	110
8	41/7	41/21	28	17	...	...	118/74	

been mentioned as a cause for this condition but none of the patients showed severe stigmata of malnutrition. With adequate hospital diets no change in their clinical status was observed. In a follow-up study of 109 men interned in Japanese prison camps during World War II who had clinical evidence of beriberi, the few instances of cardiac enlargement that occurred during a five-year period were not the sequelae of nutritional deficiencies.[11] Moreover, clinical and necropsy studies of malnourished individuals from prison and concentration camps have shown that atrophic rather than hypertrophic hearts were the rule.[12]

The association of portal cirrhosis and idiopathic cardiac enlargement has been described by Lunseth et al.[13] They observed that twelve of 108 patients dying from portal cirrhosis showed enlarged hearts in which arteriosclerosis, hypertension and valvular lesions could be satisfactorily excluded. From data obtained from the study of dogs Cohn[14] believes that this condition is related to shunting of blood through portal to pulmonary venous anastomoses.

DIFFERENTIAL DIAGNOSIS

Although the clinical diagnosis of idiopathic myocardial hypertrophy ultimately rests on exclusion of the various conditions that simulate it, certain clinical features strongly point toward this diagnosis. Most of the patients are males and symptoms usually develop during the third and fourth decades.[3] It is not uncommon to obtain a history of cardiac enlargement discovered during routine examinations several months or years prior to the actual onset of symptoms. Although mild antecedent upper respiratory infections are frequently recalled, these patients do not usually present evidence of an active infection when manifestations of heart malfunction develop. Alcoholism and portal cirrhosis may be associated with this disease, but the nutritional status is usually good and avitaminosis is absent.

Physical examination may reveal the signs of congestive heart failure or these may be completely absent except for cardiac enlargement. The point of maximum impulse is usually diffuse and forceful; it is located outside the midclavicular line. The rhythm is generally a sinus tachycardia but the rate slows with digitalis therapy. Gallop sounds are common but organic murmurs are not heard. The manifestations of pulmonary and systemic emboli arising from intracardiac thrombi at times dominate the clinical picture.

The following disease entities offer the greatest problems in differential diagnosis:

Chronic Constrictive Pericarditis: Both this disease and idiopathic myocardial hypertrophy frequently show intractable congestive heart failure and gallop rhythms. However, roentgenograms usually show a smaller heart in constrictive pericarditis, and up to 70 per cent have pericardial calcifications.[6] In doubtful cases cardiac catheterization may be necessary to differentiate these two conditions. In constrictive pericarditis a characteristic contour

has been found for the right ventricular pressure curves, i.e., an early diastolic dip rising to a diastolic plateau greater than one-third the systolic pressure.[15]

Coronary Artery Disease: Because of its frequency, coronary artery disease is diagnosed too readily as the cause of cardiac enlargement in normotensive patients without organic heart murmurs. It has been pointed out[16] that if cardiac hypertrophy follows coronary occlusion, it is due to pre-existing hypertension, associated valvular disease or to congestive heart failure caused by extensive myocardial damage. The presence of myocardial infarction does not necessarily negate the diagnosis of idiopathic myocardial hypertrophy provided it can be established that cardiac enlargement existed before the infarction.[17] The causes of the infarction may be due to coexisting coronary artery disease with relative anoxia to the hypertrophied muscle or to coronary embolism arising from intramural thrombi. It should be noted that true anginal pain and hypercholesterolemia are rare in cases of idiopathic myocardial hypertrophy.

Myocarditis: Myocarditis produced by known infectious agents is often only a pathologic-anatomic diagnosis since the lesions may be overshadowed by other clinical features of the disease.[16] Although acute idiopathic myocarditis can be distinguished pathologically from idiopathic myocardial hypertrophy by interstitial cellular infiltration, the clinical courses of both conditions may be quite similar. Systemic signs of infection or toxicity, when present, may be the only distinguishing features.

Amyloidosis: This often poses a difficult differential problem since approximately 60 per cent of these cases reveal congestive heart failure, often of an intractable nature. However, the age of its onset is usually later than that of idiopathic myocardial hypertrophy, the peak being in the sixth and seventh decades.[18] The atria are nearly always affected and atrial arrhythmias are particularly common. Amyloid hearts have the smallest increase in weight among the cardiomyopathies, most of them weighing between 400 and 600 gm.[6] Signs of systemic amyloidosis, such as skin deposits, macroglossia, polyneuropathy, plasmacytosis and an abnormal alpha-2 globulin fraction, may point the way to the diagnosis. Unfortunately, the Congo red test is usually negative owing to this dye's poor affinity for the amyloid deposited in the myocardium.[19]

Collagen Diseases: Except for scleroderma, cardiac involvement does not usually occur as an isolated finding in this group of diseases. Moreover, early in the course of scleroderma most of the cardiopulmonary disability is produced by restrictive lung disease and impairment in gaseous diffusion. Severe myocardial disease with intractable congestive heart failure occurs late in the disease when the full blown picture of scleroderma is fairly evident.[20]

Endocardial Fibroelastosis: This disease cannot usually be differentiated clinically from idiopathic myocardial hypertrophy because of their exact courses. Pathologically, although endocardial thickening may be present in cases of idiopathic myocardial hypertrophy, the elastic tissue shows broken, irregular masses in contrast to the proliferating even layers of elastic tissue in endocardial fibroelastosis.[21,22] In some cases of endocardial fibroelastosis the endocardial thickening may produce a restriction in diastolic filling, resulting in ventricular pressure curves mimicking those of constrictive pericarditis.[23]

Summary

The records of twenty-one patients with idiopathic myocardial hypertrophy observed during a period of five years were reviewed. On the basis of their dominant clinical course these cases could be classified into three groups: (1) severe intractable congestive heart failure; (2) minimal to moderate congestive heart failure; (3) symptoms referable primarily to an associated portal cirrhosis. The cause of this disorder remains obscure. However, in the first two groups there is speculation that some of the cases might be congenital in origin.

The clinical features were related to the underlying congestive heart failure and to pulmonary and systemic emboli which at times dominated the picture. The electrocardiogram in typical cases showed left ventricular hypertrophy or intraventricular conduction disturbances, normal or left axis deviation and a characteristic biphasic P wave in lead V_1. Roentgenograms of the chest showed globular cardiac enlargement. Cardiac catheterization and ballistocardiographic data were consistent with congestive heart failure.

Histologic examination of the heart revealed myocardial hypertrophy usually associated with focal interstitial fibrosis. Over one half of cases undergoing necropsy revealed intramural thrombi in the left ventricle.

The possible etiologic factors and the dif-

ferential diagnosis of this condition were considered. The diagnosis of idiopathic myocardial hypertrophy is suggested by the presence of cardiomegaly in relatively young normotensive adults with gallop sounds, absent organic murmurs and electrocardiographic criteria of both left atrial and left ventricular enlargement irrespective of the presence or absence of congestive phenomena.

References

1. Elster, S. K., Horn, H. and Tuchman, L. R. Cardiac hypertrophy and insufficiency of unknown etiology: a clinical and pathologic study of 10 cases. *Am. J. Med.*, 18: 900, 1955.
2. McNamara, P. J., Jacobs, W. H. and Jaffe, R. J. Idiopathic cardiac hypertrophy with endomyocardial fibrosis: report of a case developing after recovery from a purulent lung abscess. *Ann. Int. Med.*, 50: 1035, 1959.
3. Spodick, D. H. and Littman, D. Idiopathic myocardial hypertrophy. *Am. J. Cardiol.*, 1: 610, 1958.
4. Croxton, F. E. Elementary Statistics with Application in Medicine, p. 267. New York, 1953. Prentice-Hall.
5. de Olivera, J. M. and Zimmerman, H. A. Auricular overloadings: electrocardiographic analysis of 193 cases. *Am. J. Cardiol.*, 3: 453, 1959.
6. Brigden, W. Uncommon myocardial diseases: the non-coronary cardiomyopathies. *Lancet*, 2: 1179, 1243, 1957.
7. Campbell, M. and Turner-Warwick, M. Two more families with cardiomegaly. *Brit. Heart J.*, 18: 393, 1956.
8. Evans, W. Familial cardiomegaly. *Brit. Heart J.*, 11: 68, 1949.
9. Gaunt, R. T. and Lecutier, M. A. Familial cardiomegaly. *Brit. Heart J.*, 18: 251, 1956.
10. Moghadam, A. N. Personal communication.
11. Griffith, R. L. Condition of the heart following beriberi and malnutrition. *Arch. Int. Med.*, 89: 743, 1952.
12. Ellis, L. B. Electrocardiographic abnormalities in severe malnutrition. *Brit. Heart J.*, 8: 53, 1946.
13. Lunseth, J. H., Olmstead, E. G. and Abbound, F. A study of heart disease in one hundred eight hospitalized patients with portal cirrhosis. *Arch. Int. Med.*, 102: 405, 1950.
14. Cohn, R. The relationship of cardiac hypertrophy to cirrhosis of the liver. *Surgery*, 46: 887, 1959.
15. Khalil, S. A. and Lewis, D. H. Chronic constrictive pericarditis. (In preparation.)
16. Friedberg, C. K. Diseases of the Heart, 2nd ed., p. 504. Philadelphia, 1956. W. B. Saunders Co.
17. Case 45251. *New England J. Med.*, 260: 1283, 1959.
18. Benson, R. and Smith, J. F. Cardiac amyloidosis. *Brit. Heart J.*, 18: 529, 1956.
19. Osserman, E. F. Plasma-cell myeloma. II. Clinical aspects. *New England J. Med.*, 261: 952, 1006, 1959.
20. Sackner, M. A., Kimbel, P., Glauser, E. M. and Lewis, D. H. Cardiopulmonary studies in scleroderma. *Clin. Res.*, 7: 239, 1959.
21. Davies, J. N. P. and Bell, J. D. The pathology of endomyocardial fibrosis in Ugandi. *Brit. Heart J.*, 17: 337, 1955.
22. Thomas, W. A., Randall, R. V., Bland, E. F. and Castleman, B. Endocardial fibroelastosis: a factor in heart disease of obscure etiology. *New England J. Med.*, 251: 327, 1954.
23. Van Buchem, F. S. P., Arends, A. and Schroder, E. A. Endocardial fibroelastosis in adolescents and adults. *Brit. Heart J.*, 21: 229, 1959.

Case Reports

Resuscitation from Ventricular Fibrillation Complicating Acute Coronary Occlusion*

Report of a Case

ELLIS L. ROLETT, M.D.†

Boston, Massachusetts

RESUSCITATION FROM ventricular fibrillation has had the attention of physiologists for the past sixty years but successful defibrillation of the human ventricle has only been accomplished in recent years.[1] It has long been known that the viability of the heart muscle succeeds cessation of the heart beat at death. The heart muscle retains its intrinsic ability to contract for many hours after death and rhythmic contractions may be restored by mechanical stimulation.[2] This property of the heart muscle forms the basis of success in all cardiac resuscitative procedures.

The purpose of this paper is to emphasize the fundamental logic of cardiac resuscitation in ventricular fibrillation secondary to acute coronary occlusion and to report a case of successful resuscitation in acute coronary occlusion complicated by ventricular fibrillation. Detailed descriptions of the technic of open chest cardiac resuscitation are available elsewhere.[3]

PHYSIOLOGIC CONSIDERATIONS

Cardiac arrest leads to the immediate cessation of effective circulation. It may be due to either ventricular fibrillation or ventricular standstill. Systemic and coronary vessel blood flow during ventricular fibrillation is inconsequential.[4] With the exception of specific conditions in which spontaneous recovery sometimes occurs, ventricular fibrillation is usually fatal in the larger mammals, including man.

Few statistics are available on the relative occurrence of ventricular fibrillation and ventricular standstill when cardiac arrest follows acute coronary occlusion. Experimental ligation of a major coronary artery in dogs resulted in an incidence of ventricular fibrillation as high as 70 per cent.[5] Ventricular fibrillation seems to be the mechanism of sudden death occurring in the first few days following the occlusion of the coronary artery in a significant proportion, perhaps even the majority, of human patients.[6,7] Statistics derived from 866 United States Army personnel between the ages of eighteen and thirty-nine years who suffered acute coronary occlusions during World War II have been published.[8] Fifty-two per cent of this group died and were autopsied. Of the fatal cases, death occurred within twenty-four hours of the onset of symptoms in 83 per cent and pathologic examination disclosed no myocardial infarction in 70 per cent. The absence of myocardial necrosis suggests that cardiac arrest was the cause of death. Ischemic myocardium is more susceptible to ventricular fibrillation; a possible explanation of this has been offered.[9]

In order to judge the results of resuscitative procedures, the infrequency of spontaneous recovery from ventricular fibrillation should be emphasized. In a series of 208 dogs there was not a single spontaneous recovery from ventricular fibrillation.[10] There have been only isolated reports with electrocardiographic evidence of spontaneous recovery in man and

* From the Medical Service of the 7520th U. S. Air Force Hospital, South Ruislip, England.

† Present address: Department of Cardiology, Massachusetts General Hospital, Boston, Massachusetts.

TABLE I
Reported Cases of Coronary Occlusion and Ventricular Fibrillation with Resuscitation

Reference*	Age (years)	Onset of Ventricular Fibrillation† (hours)	Duration of Ventricular Fibrillation before Cardiac Massage Begun (minutes)	Length of Survival	Mental Status
Reagan et al.[33]	55	Over 1	Less than 2	Well, 4 years later[36]	Amnesia for the day before ventricular fibrillation
Celio[34]	46	Less than 24	2 to 3	Well, 4 months later	Amnesia for events before ventricular fibrillation
Beck et al.[35]	65	24	5	Well, 2 years later[36]	Amnesia for the events of resuscitation
Bloomfield and Mannick[36]	41	2½	Unknown	Well, 2 years and 3 months later‡	No deficits
McGregor and Newton[37]	51	1½	1	Well, 18 months later	No deficits
Nickel and Gale[38]	53	Several hours§	2 to 3	Well, 6 months later	Amnesia for the day before ventricular fibrillation
Nickel and Gale[38]	40	Not stated§	3	Well, 5 months later	No deficits
Conklin et al.[39]	51	Over 1	4½	Well, 9 months later	Amnesia for 5 days after resuscitation
Rolett	34	29	1½ to 2	Well, as of writing	Amnesia for the 3 hours before fibrillation

* All patients were men. Available evidence indicates that each of these patients was experiencing his first acute coronary occlusion.

† This is the interval between the start of the prolonged ischemic chest pain and the onset of ventricular fibrillation.

‡ Review of the hospital record reveals that the patient was symptom-free and working at the time of his last clinic visit two years and three months following resuscitation.

§ Ventricular standstill was present when thoracotomy was performed, this rhythm being replaced by ventricular fibrillation shortly thereafter.

as a rule these cases have demonstrated an atrioventricular or intraventricular conduction defect before the episode of ventricular fibrillation.[11–13] The relationship between recurring transient ventricular fibrillation and a conduction defect was recognized years ago and is an example of the Adams-Stokes syndrome.[14] Two cases in which transient fibrillation occurred in the absence of a conduction defect have been reported,[15,16] but the existence of true ventricular fibrillation in one of these has been doubted.[17]

Wiggers has summarized the work leading to the development of an effective technic for dealing with ventricular fibrillation produced experimentally by coronary artery ligation or electrocution.[18] This method has proved almost without exception to result in the restoration of normal circulatory dynamics in the experimental dog if begun within four minutes of the onset of fibrillation. The technic employs rhythmic compression of the heart in association with oxygenation of the lungs. The ventricle is then defibrillated by means of an electric shock applied directly to its surface. Drugs have not been useful in the termination of this arrhythmia. Oxygenation of the myocardium during ventricular fibrillation is necessary for preservation of the intrinsic rhythmicity and contractility of the heart muscle. Defibrillation of the anoxic heart results in an ineffective heart beat or none at all.[19] Hence, both cardiac compression and artificial respiration are essential parts of the resuscitative procedure.

Resuscitation in Clinical Situations

The history of the successful application of the method of open chest cardiac resuscitation to clinical situations has been traced by Southworth.[20] The initial successes were in the operating room. Since 1956 seven reports have

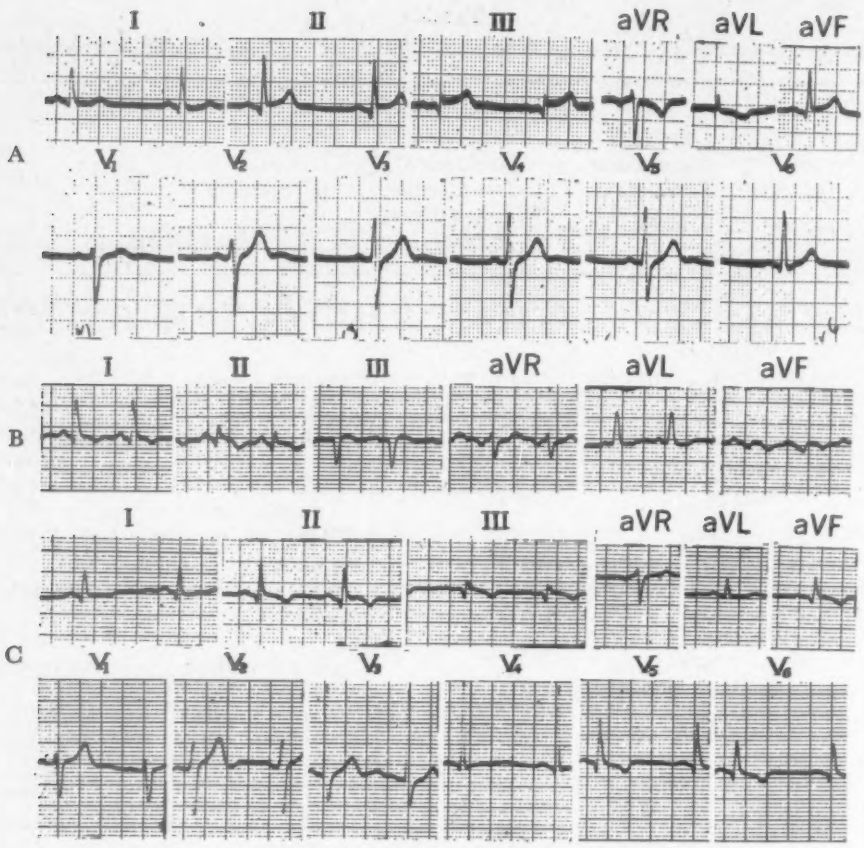


FIG. 1. Electrocardiograms showing evolution of an inferior myocardial infarction. A, taken March 11, 1959, before onset of ventricular fibrillation. Small Q waves and S-T segment elevation in leads II, III and aVF. B, taken March 13, 1959, following resuscitation. Deepening of Q wave in lead II, loss of R wave in leads III and aVF and T wave inversion in leads I, II, III and aVF. C, taken April 30, 1959, after convalescence. Return of R wave in III and aVF, and residual T wave inversion in lead II, III, aVF, V_5 and V_6.

appeared describing the resuscitation of eight patients from death due to ventricular fibrillation complicating acute coronary occlusion (Table I). To these reported cases we add the following case.

CASE REPORT

A thirty-four year old man, a noncommissioned officer, was admitted to the Medical Service of the 7520th USAF Hospital on March 11, 1959 with the complaint of substernal pain. He had been in good health until two weeks before admission when he experienced a brief substernal sensation of pressure during exercise. Twenty-four hours before admission the same sensation recurred after a large meal. On this occasion it became more intense, radiated to both arms and the jaw, was not relieved by meperidine and persisted for over twelve hours. An electrocardiogram performed at a base dispensary revealed small Q waves and elevation of the S-T segments in leads II, III and aVF (Fig. 1A). A roentgenogram of the chest was within normal limits. He was transferred to the 7520th USAF Hospital.

Physical Examination: The patient appeared acutely uncomfortable and apprehensive. The temperature, blood pressure, pulse and respirations were normal. There were no notable findings in the head or neck and the lungs seemed normal. The heart was not enlarged and the rhythm was regular. There were no abnormal cardiac findings.

Laboratory Data: Studies on admission included a white blood cell count of 19,500 per cu. mm., 59 per cent of which were neutrophils, an hematocrit of 46 per cent, normal urinalysis and a serum glutamic oxaloacetic transaminase of 23 units (normal, 5 to 40 units). An electrocardiogram indicated further changes of an acute inferior myocardial infarction with a normal rhythm.

Cardiac Arrest and Resuscitation: Five hours after admission the patient was comfortable and alert and had a regular radial pulse. Five minutes later he suddenly began to convulse. The ward physician came at that moment. The diagnosis of cardiac arrest was

immediately evident on the basis of unconsciousness, agonal respirations and absent heart beat. With the aid of a scalpel and rib spreader maintained in readiness on the ward, an immediate unsterile thoracotomy was performed in bed. There was no bleeding and a direct view of the heart disclosed that the ventricles were fibrillating. Simultaneously with the thoracotomy, mouth-to-mouth artificial respiration was effectively instituted by the ward nurse. Compression of the heart through the intact pericardium against the rear of the sternum was begun an estimated ninety seconds from the onset of the convulsion and a rate of approximately sixty times a minute was maintained. The heart muscle tone was excellent and the cyanotic heart and tissues of the lung became pink. Carotid artery pulsations were palpable with manual systole. Within several minutes the patient began thrashing his limbs and spontaneous respirations returned. Endotracheal intubation was performed after twenty minutes when the anesthesiologist and surgeon arrived. The resultant improvement in oxygenation was accompanied by a higher level of consciousness. (The patient was later able to recall the latter events of the resuscitative procedure.) After forty-seven minutes of manual compression, a defibrillatory shock of 150 volts of 0.15 second duration was delivered by electrodes in direct contact with the heart.* The result was an immediate tonic contraction of the entire heart for two seconds superseded by regular rhythmic contractions. Throughout this resuscitative procedure no drugs were used.

A normal blood pressure was thereafter maintained spontaneously. An electrocardiogram thirty minutes after defibrillation exhibited a rapid idioventricular rhythm which was followed five minutes later by a regular sinus rhythm. The thoracotomy wound was closed with the aid of nitrous oxide anesthesia. The patient regained full consciousness within five minutes of the closure of the chest. He was then digitalized and given maintenance doses of procaine amide and prophylactic penicillin.

Clinical Course: The immediate postoperative phase was smooth. The transaminase rose to a peak of 81 units two days after admission and then returned to normal. Serial electrocardiograms revealed a normal sinus rhythm and an evolving inferior myocardial infarction (Fig. 1B). No myocardial irritability was detected on continuous oscilloscopic monitoring. Two days after resuscitation, anticoagulation was instituted. Convalescence was complicated by a left thoracic empyema, organism unknown, which became manifest on the ninth postoperative day and cleared over a two-week period of vigorous antibiotic therapy.

The patient was gradually ambulated. His final electrocardiogram indicated residual findings of an inferior myocardial infarction (Fig. 1C) and the roentgenogram of the chest demonstrated left pleural adhesions and thickening (Fig. 2). The neurologic status was completely normal except for a period of amnesia covering the three hours prior to the onset of ventricular fibrillation. The patient was discharged on the fifty-fourth hospital day. His over-all condition was good and no medications were required.

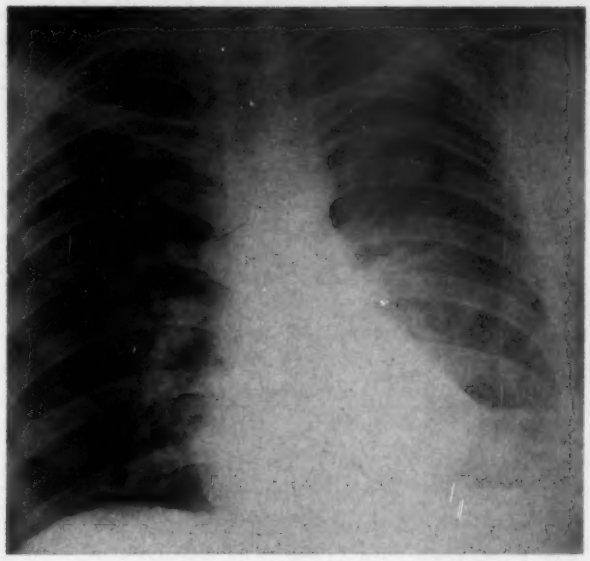


FIG. 2. Roentgenogram of the chest taken April 27, 1959 seven weeks following thoracotomy. There is scarring and adhesions at the base of the left lung.

Less than five months later he began operating his own gas station and at the time of the last communication two years after defibrillation he was working more than twelve hours daily without undue fatigue or adverse symptoms.

COMMENTS

This case represents an instance of prompt restitution of effective coronary and cerebral circulation sufficiently early after the onset of ventricular fibrillation for survival to be possible. No drugs were needed for defibrillation. The facts that only a single shock was required to defibrillate the ventricle and that an effective, regular beat took over immediately are evidence that the myocardium had been adequately oxygenated. Hence, the rhythmicity, excitability and contractility of the heart were preserved.

A tabulation of some features of the reported cases of successful resuscitation following acute coronary occlusion with ventricular fibrillation reveals some noteworthy points (Table 1). All the patients in this study have been men between ages thirty-four and sixty-five years who were presumably experiencing such an occlusion for the first time. Ventricular fibrillation was a complication suffered by this group

* Electrodyne Defibrillator, Electrodyne Company, Norwood, Massachusetts.

TABLE II
Survival Rates: External Defibrillation in Dogs

Reference	Duration of Ventricular Fibrillation (seconds)	Number of Dogs	Number Surviving	Per Cent Surviving
Kouwenhoven et al.[25]	30	224	221	99
	60	68	61	90
	90	68	26	38
Hosler and Wolfe[26]	15 to 35	10	9	90
	45 to 60	18	7	39
	65 to 90	23	4	17

in common during the first day subsequent to the onset of pain in the chest. Cardiac massage was instituted in bed no later than five minutes in any case and within three minutes in the majority after the presumed onset of ventricular fibrillation. Prolonged survivals up to four years after the event have been noted. There were no instances of postoperative deaths or important damage to the central nervous system.

Restoration of effective circulation within four minutes of the onset of circulatory arrest was necessary to prevent serious disturbances in the central nervous system of the cat[21] and to prevent death in the human subject.[22,23] Meeting this deadline is dependent upon the prompt recognition of cardiac arrest by the signs of unconsciousness, cessation of arterial pulsations and heart sounds, apnea, asphyxial respiratory gasps and convulsions. Unconsciousness occurs approximately ten to twenty seconds, and apnea or convulsions forty seconds, after cardiac arrest. These signs do not distinguish ventricular fibrillation from ventricular standstill but no time can be spent making the distinction electrocardiographically.

External Electrical Defibrillation: The experimental work of Wiggers and others established the physiologic soundness of open chest resuscitation in the dog.[18] The development of an equally sound technic which does not necessitate thoracotomy would provide the advantage of sparing both the patient and his physician the trauma of an unsterile major surgical procedure. Electrical defibrillation of the heart through the intact wall of the chest has been investigated in dogs and larger mammals in which ventricular fibrillation was induced by small electric shocks. Fibrillation could be terminated if a sufficiently large countershock was administered within one minute of the onset of the arrhythmia.[24] However, it must be emphasized that the ability to defibrillate a heart does not necessarily mean that the animal survives. The heart may be externally defibrillated but the dog may die because effective cardiac contractions do not resume. Actual figures indicate that the survival rate drops off sharply when ventricular fibrillation lasts longer than forty-five to sixty seconds before the external electric shock is applied (Table II).

These observations point to the inherent limitations of a resuscitative procedure which does not provide for the oxygenation of the myocardium. In the absence of cardiac compression the permissible delay between the onset of ventricular fibrillation and the administration of the countershock is reduced to one minute or less if success is to be achieved.[25,26] In sharp contrast, studies with dogs show that fibrillation can be allowed to persist for five minutes with subsequent revival of the animal if open chest resuscitative measures are then put into effect.[27] The experience with human subjects in situations of coronary occlusion, anesthesia and surgery support these points[22,23] (Table I). Once cardiac compression has been started the remainder of the defibrillatory maneuver may be carried out in unhurried fashion.

Attempts at external electric defibrillation without cardiac massage have met with success only in specific circumstances in the human being. The reports of survival fall into two categories. The first is comprised of a group of patients with complete heart block in whom episodes of transient self-limiting ventricular fibrillation occurred along with episodes that responded to external shock.[25,28,29] The second group is comprised of four patients with congenital cardiac anomalies, three of whom were infants aged three months or younger, in whom ventricular fibrillation developed during cardiac catheterization.[25,30] Various observations suggest that the electrophysiology of ventricular fibrillation in these two circumstances differs from that of ventricular fibrillation consequent to coronary occlusion. Reference has been made previously to the transience of ventricular fibrillation in association with atrioventricular conduction defects. Spontaneous cessation of ventricular fibrillation also occurs in the smaller mammals such as the cat and rabbit but not in the larger ones such as the dog.[31] Hence, small heart mass may interfere with the perpetuation of fibrillatory impulses and thereby lead to impermanence of the arrhythmia.

Closed Chest Cardiac Massage: Recently the experience with a newly devised technic has been reported from Johns Hopkins Hospital.[32] This method eliminates the need for thoracotomy and direct cardiac massage. Instead it has been demonstrated that rhythmic pressure applied to the sternum of the intact thorax can compress the heart sufficiently to produce an effective cardiac output. By means of this closed chest cardiac massage, three patients with ventricular fibrillation were successfully defibrillated with an externally applied electric shock. One of these patients had suffered an acute coronary occlusion.

This technic for closed chest cardiac compression has been used in a limited number of instances of cardiac standstill at the Massachusetts General Hospital. In some of these cases restoration of effective heart action has been achieved. It is our impression that stronger peripheral arterial pulsations can be produced by closed chest sternal pressure than by direct cardiac massage. This may be due to better diastolic filling of the ventricles because of the existence of negative intrathoracic pressure between periods of manually induced systole.

Indications for Resuscitative Measures: A prerequisite for successful cardiac resuscitation is a preconceived plan of action so that the four minute limit is not violated. Further experience with the system of closed chest cardiac massage is needed to determine whether it deserves preference over the open chest procedure. Employment of external electric currents without cardiac compression may consume precious minutes which might otherwise be utilized in the institution of cardiac massage.

Thoracotomy should not be carried out if the fundamental health of the person does not justify the restoration of life and if the cardiac arrest is known to be of more than four minutes' duration.

Once the indication for resuscitative measures is apparent cardiac compression is best initiated by the physician at the scene before recourse to electrocardiographic proof, alternative resuscitative measures or the summoning of a surgeon.

Summary

Ventricular fibrillation is a frequent complication during the twenty-four hours after acute coronary occlusion. This arrhythmia invariably results in death. A method for defibrillation of the ventricle has been developed and the successful employment of this in man has been reported in recent years. The procedure includes thoracotomy and rhythmic compression of the heart in association with artificial respiration. It must be instituted within a time limit of approximately four minutes after the onset of ventricular fibrillation. Adequate myocardial oxygenation is a requirement for success and is dependent equally upon effective artificial respiration and effective cardiac compression. The ventricle is then defibrillated by means of electric shock applied directly to the heart.

What is believed to be the ninth reported case of successful open chest cardiac resuscitation in acute coronary occlusion complicated by ventricular fibrillation is recorded here.

External electric defibrillation through the intact chest wall without cardiac massage is useful mainly when ventricular fibrillation occurs in a setting of complete heart block. The newly developed technic of closed chest cardiac compression may extend the usefulness of external electric shock to cases of ventricular fibrillation secondary to acute coronary occlusion.

It should be emphasized that the development of ventricular fibrillation does not itself signify an irreversibly damaged heart but may instead be a chance occurrence in a relatively healthy heart. This constitutes a potentially salvagable condition. The employment of cardiac resuscitation by the physician is encouraged when acute coronary occlusion is complicated by ventricular fibrillation.

References

1. Beck, C. S., Pritchard, W. H. and Feil, H. S. Ventricular fibrillation of long duration abolished by electric shock. *J.A.M.A.*, 135: 985, 1947.
2. Kountz, W. B. Revival of human hearts. *Ann. Int. Med.*, 10: 330, 1936–37.
3. Beck, C. S. and Rand, H. J., III. Cardiac arrest during anesthesia and surgery. *J.A.M.A.*, 141: 1230, 1949.
4. Corday, E., Gold, H., de Vera, L. B., Williams, J. H. and Fields, J. Effect of the cardiac arrhythmias on the coronary circulation. *Ann. Int. Med.*, 50: 535, 1959.
5. Brofman, B. L., Leighninger, D. S. and Beck, C. S. Electric instability of the heart: the concept of the current of oxygen differential in coronary artery disease. *Circulation*, 13: 161, 1956.
6. Miller, H. Ventricular fibrillation as the mechanism of sudden death in patients with coronary occlusion. *New England J. Med.*, 221: 564, 1939.
7. Stroud, M. W. and Feil, H. S. The terminal electrocardiogram: twenty-three case reports and a review of the literature. *Am. Heart J.*, 35: 910, 1948.

8. YATER, W. M., TRAUM, A. H., BROWN, W. G., FITZGERALD, R. P., GEISLER M. A. and WILCOX, B. B. Coronary artery disease in men eighteen to thirty-nine years of age. *Am. Heart J.*, 36: 334, 481, 683, 1948.
9. WIGGERS, C. J., WÉGRIA, R. and PIÑERA, B. The effects of myocardial ischemia on the fibrillation threshold. The mechanism of spontaneous ventricular fibrillation following coronary occlusion. *Am. J. Physiol.*, 131: 309, 1940.
10. WIGGERS, C. J. Studies of ventricular fibrillation caused by electric shock. I. The revival of the heart from ventricular fibrillation by successive use of potassium and calcium salts. *Am. J. Physiol.*, 92: 223, 1930.
11. ROBINSON, G. C. and BREDECK, J. F. Ventricular fibrillation in man with cardiac recovery. *Arch. Int. Med.*, 20: 725, 1917.
12. SCHWARTZ, S. P. Studies on transient ventricular fibrillation. IV. Observations on the clinical and graphic manifestations following the revival of the heart from transient ventricular fibrillation. *Am. J. M. Sc.*, 192: 808, 1936.
13. ZIMDAHL, W. T. and FULTON, F. T. Transient ventricular fibrillation. Report of a case with spontaneous recovery. *Am. Heart J.*, 32: 117, 1946.
14. DAVIS, D. and SPRAGUE, H. B. Ventricular fibrillation: its relation to heart block. *Am. Heart J.*, 4: 559, 1929.
15. THOMPSON, S. A., BIRNBAUM, G. L. and SHINER, I. S. Cardiac resuscitation with report of a case of successful resuscitation following auricular and ventricular fibrillation. *J.A.M.A.*, 119: 1479, 1942.
16. DANIEL, F. D. and MAGRUDER, R. G. Report of a case of ventricular fibrillation with recovery following acute coronary occlusion. *Am. Heart J.*, 39: 451, 1950.
17. FAUTEUX, M. Cardiac resuscitation. *J. Thoracic Surg.*, 16: 623, 1947.
18. WIGGERS, C. J. Editorial. Defibrillation of the ventricles. *Circulation Res.*, 1: 191, 1953.
19. LAPE, H. E. and MAISON, G. L. Cardiac resuscitation and survival. Influence of rate of manual compression, type of countershock, and of epinephrine. *Am. J. Physiol.*, 172: 417, 1953.
20. SOUTHWORTH, H. The resuscitation problem. *Circulation*, 20: 946, 1959.
21. WEINBERGER, L. M., GIBBON, M. H. and GIBBON, J. H., JR. Temporary arrest of the circulation to the central nervous system. I. Physiologic effects. *Arch. Neurol. & Psychiat.*, 43: 615, 1940.
22. STEPHENSON, H. E., JR., REID, L. C. and HINTON, J. W. Pitfalls, precautions, and complications in cardiac resuscitation. Study of 1,200 cases. *Arch. Surg.*, 69: 37, 1954.
23. COLE, S. L. and CORDAY, E. Four-minute limit for cardiac resuscitation. *J.A.M.A.*, 161: 1454, 1956.
24. GUYTON, A. C. and SATTERFIELD, J. Factors concerned in electrical defibrillation of the heart, particularly through the unopened chest. *Am. J. Physiol.*, 167: 81, 1951.
25. KOUWENHOVEN, W. B., MILNOR, W. R., KNICKERBOCKER, G. G. and CHESNUT, W. R. Closed chest defibrillation of the heart. *Surgery*, 42: 550, 1957.
26. HOSLER, R. M. and WOLFE, K. Closed-chest resuscitation. *Arch. Surg.*, 79: 31, 1959.
27. WIGGERS, C. J. Cardiac massage followed by countershock in revival of mammalian ventricles from fibrillation due to coronary occlusion. *Am. J. Physiol.*, 116: 161, 1936.
28. ZOLL, P. M., LINENTHAL, A. J., GIBSON, W., PAUL, M. H. and NORMAN, L. R.: Termination of ventricular fibrillation in man by externally applied electric countershock. *New England J. Med.*, 254: 727, 1956.
29. ZOLL, P. M., LINENTHAL, A. J. and ZARSKY, L. R. N. Ventricular fibrillation. Treatment and prevention by external electric currents. *New England J. Med.*, 262: 105, 1960.
30. SASAHARA, A. A., RUDOLPH, A. M., HOFFMAN, J. I. E. and HAUCK, A. J. Ventricular fibrillation during catheterization of the right side of the heart terminated successfully by external defibrillation. *New England J. Med.*, 261: 26, 1959.
31. MCWILLIAM, J. A. Fibrillar contraction of the heart. *J. Physiol., London*, 8: 296, 1887.
32. KOUWENHOVEN, W. B., JUDE, J. R. and KNICKERBOCKER, G. G. Closed chest cardiac massage. *J.A.M.A.*, 173: 1064, 1960.
33. REAGAN, L. B., YOUNG, K. R. and NICHOLSON, J. W. Ventricular fibrillation in a patient with probable acute coronary occlusion. *Surgery*, 39: 482, 1956.
34. CELIO, A. Cardiac arrest associated with coronary occlusion: successful resuscitation. *J. Internat. Coll. Surgeons*, 25: 299, 1956.
35. BECK, C. S., WECKESSER, E. C. and BARRY, F. M. Fatal heart attack and successful defibrillation. *J.A.M.A.*, 161: 434, 1956.
36. BLOOMFIELD, D. K. and MANNICK, J. A. Successful resuscitation in acute myocardial infarction with ventricular fibrillation. Report of a case. *New England J. Med.*, 258: 1244, 1958.
37. MCGREGOR, J. G. and NEWTON, D. E. The treatment of cardiac arrest following myocardial infarction. *U. S. Armed Forces M. J.*, 10: 125, 1959.
38. NICKEL, S. N. and GALE, H. H. Altered prognosis with cardiac massage. Cardiac resuscitation in acute myocardial infarction. Report of two successfully treated cases. *J.A.M.A.*, 170: 23, 1959.
39. CONKLIN, W. H., BEEBE, R. T. and FRAWLEY, T. F. Ventricular fibrillation due to myocardial infarction with survival. *Arch. Int. Med.*, 104: 281, 1959.

Closed Chest Cardiac Resuscitation in Acute Myocardial Infarction*

F. Joseph Thal, M.D., F.A.C.C., Maria E. Cerny, M.D., Donald J. Conlon, M.D., Marvin A. Yussman, M.D. *and* Robert H. Irwin, M.D.

San Francisco, California

Sudden death caused by ventricular standstill or ventricular fibrillation has, until recently, almost always been an irreversible catastrophe. In certain circumstances, patients may now be resuscitated from "clinical death" by means of cardiac massage and defibrillation. Open chest cardiac massage has been used with increased frequency since the advent of cardiac surgery but the use of this method outside of the operating room is generally unsatisfactory as well as hazardous.

Closed chest cardiac massage, described by Kouwenhoven and associates,[1] is now accessible to medical and nursing personnel. The technic is easy to learn and requires no special equipment. It has made obsolete previously tried but rarely successful methods of external cardiac stimulation such as blows on the chest, recently reviewed by Scherf and Bornemann.[2] Electric stimulation and defibrillation of the heart have been developed mainly through the work of Zoll and associates.[3] Compact, reliable instruments for this purpose are now available. In cardiac standstill, cardiac massage alone may reestablish cardiac function; whereas in ventricular fibrillation the addition of defibrillation is required. Either method must be applied immediately; otherwise, cardiac reactivation will fail or irreversible brain damage will have occurred. It is for this reason that fortunate circumstances are requisite; i.e., medical personnel must be present at the moment of the cardiac catastrophe and a defibrillator and other equipment for resuscitation (airway, oxygen, vasopressor drugs, etc.) must be immediately available.

These circumstances prevailed in the following case and enabled us to resuscitate a patient who would have been pronounced dead by older standards.

Case Report

A forty-five year old white man had suffered an acute posterior wall myocardial infarction in 1955, from which he recovered without complication. He was seen during the intervening years on rare occasions when he complained of atypical retrosternal and epigastric pain, occurring especially under emotional stress. Electrocardiograms showed decreasing sequelae of the old posterior wall myocardial infarction (Fig. 1A). The results of other tests were equally unremarkable. Mild sedation relieved his symptoms.

On the morning of December 5, 1960, he complained of severe pain in the anterior part of the chest radiating to both arms, of approximately twelve hours' duration. He said that he had suffered from epigastric pain, nausea and occasional vomiting for the last few days. An electrocardiogram taken immediately (about 9:30 A.M.) was compatible with recent anteroseptal myocardial infarction; some ventricular premature beats were also present (Fig. 1B). The patient was immediately sent to the Kaiser Foundation Hospital, which is in close proximity to the office where he had been seen. On arrival at the hospital his pulse rate was 70 per minute with occasional premature beats. Blood pressure was at his usual level, 120/80 mm. Hg. The heart sounds were clear; no murmur, rub or gallop was heard. The patient complained only of mild discomfort in the chest and slight nausea. Morphine sulfate (15 mg.) was ordered and the routine management started. About one hour later an intern was taking his history; the patient was speaking freely and appeared to be in no distress when he suddenly stopped talking and underwent a brief convulsion; his face was flushed; pulse and heart beat were no longer detectable; he made a few, short, gasping attempts to breathe and appeared to be moribund.

* From the Department of Medicine, Permanente Medical Group, and Kaiser Foundation Hospital, San Francisco, California.

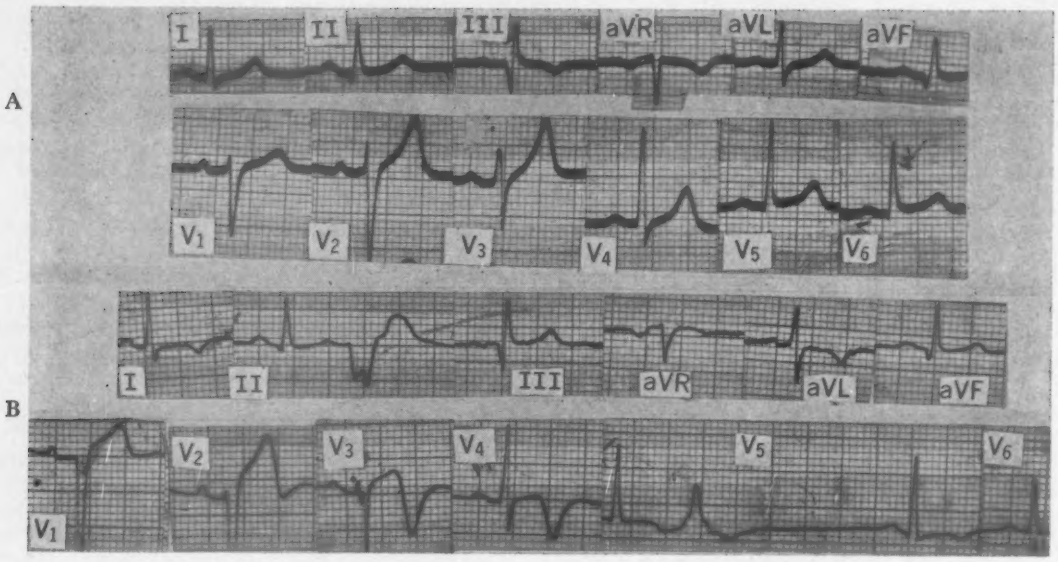


FIG. 1. A, taken December 20, 1958. Previous posterior wall myocardial infarct. B, taken December 5,1960, 9: 30 A.M. Recent anteroseptal myocardial infarct.

Cardiac Resuscitation: Closed chest cardiac massage was started immediately and help was summoned. Several other house officers and the attending physician, who were in the close vicinity, arrived within one minute. After cardiac massage was started the patient vomited copious amounts. His head was turned to the side and he was put in the shock position; an airway was inserted; oxygen was administered by hand-operated mask, interrupted by periodic tracheal suction; cardiac massage was continued. The electrocardiograph was attached; a tracing showed ventricular fibrillation (Fig. 2A). A Morris defibrillator, in the hall adjacent to the patient's room, was available without delay. A shock of "adult strength" (480 volts) was applied without effect. Cardiac massage was continued (Fig. 2B shows ventricular fibrillation and the movement of cardiac massage). A second shock of "high adult strength" (880 volts) was applied. Electrocardiographic evidence of sinus beats at the rate of approximately 50 per minute appeared, with a prolonged QRS interval of 0.16 second; some premature contractions were seen (Fig. 3A). As soon as circulation was restored, intravenous administration of l-norepinephrine was begun, maintaining a blood pressure of approximately 110/70 mm. Hg. The patient regained consciousness and looking around with amazement at the great number of doctors assembled in his room, said "I was gone, wasn't I?"

Recurrence of Ventricular Fibrillation: Several minutes later ectopic beats increased in frequency (Fig. 3B and C), followed after another few minutes by an episode of normal sinus rhythm of approximately 90 per minute and with a normal QRS of 0.08 second (Fig. 3D). An ominous electrocardiographic sign

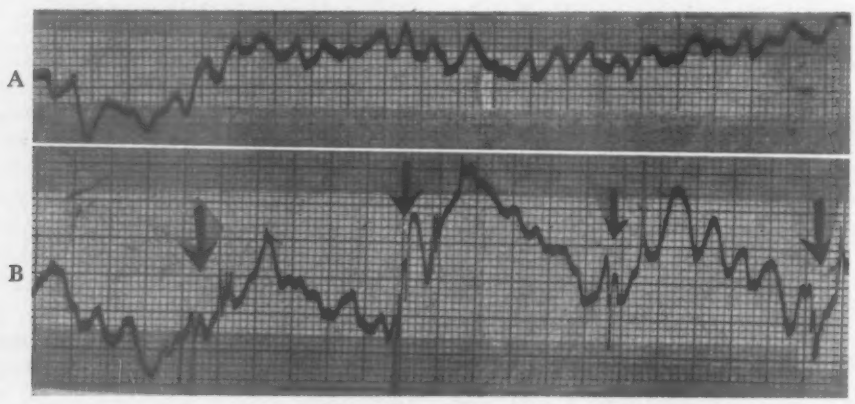


FIG. 2. A, onset of ventricular fibrillation. B, after first shock (440 volts) ventricular fibrillation continues. Deviations marked by arrows are due to cardiac massage.

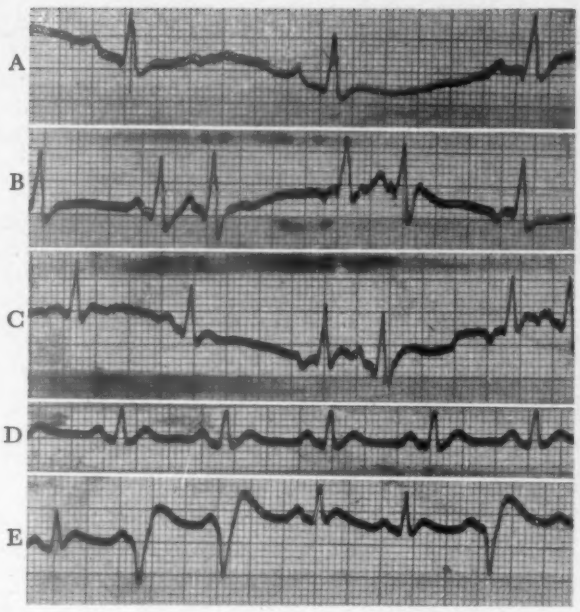


FIG. 3. A, first spontaneous beats after second shock (880 volts), regular sinus rhythm with prolonged QRS interval. B and C, frequent multifocal supraventricular ectopic beats. D, normal sinus rhythm, normal QRS interval. E, normal sinus rhythm, some complexes with aberrant conduction.

appeared shortly thereafter: frequent beats with abnormal intraventricular conduction but regular rhythm (Fig. 3E). Approximately ten minutes after the successful defibrillation ventricular fibrillation recurred (Fig. 4A) and the patient again lost consciousness. The electrocardiogram was monitored continuously; therefore, this arrhythmia was promptly recognized and a third shock of 880 volts was applied, immediately reestablishing normal sinus rhythm (Fig. 4B). Occasional premature ventricular contractions later reappeared (Fig. 4C), persisted for several days and required treatment with quinidine and procaine amide. A complete electrocardiogram taken about one hour after the third defibrillation shock (Fig. 5A) showed "increased injury pattern" with occasional ventricular premature contractions. Eight hours later (Fig. 5B) an electrocardiogram showed minor evolutionary changes of an acute anteroseptal myocardial infarct without additional damage that could be attributed to the defibrillation; in fact, this tracing differs only slightly from that taken before the patient's admission to the hospital approximately twelve hours earlier. The administration of l-norepinephrine was continued for another twelve hours, after which time the patient's blood pressure was maintained at about 110/70 mm. Hg without vasopressor drugs. Further treatment consisted of our standard therapy for acute myocardial infarction.

Subsequent Course: During the next few days the patient complained occasionally of pain in the anterior part of the chest and required small amounts of narcotics. We were unable to determine whether this pain was of coronary origin or caused by the vigorous manipulations that had been applied to his chest wall during cardiac massage. Some first degree burns appeared at the site of the defibrillator electrodes (no electrode paste had been applied, in view of the urgency of the situation) but these healed within one week. The rest of the patient's convalescence was uneventful. Serial electrocardiograms (some of which are shown in Figure 6A, B and C) showed the expected evolutionary changes. The patient was discharged from the hospital after thirty-two days.

COMMENTS

A patient who suffered his second myocardial infarction went into ventricular fibrillation without forewarning and subsequently gave all appearances of having died. Immediate ap-

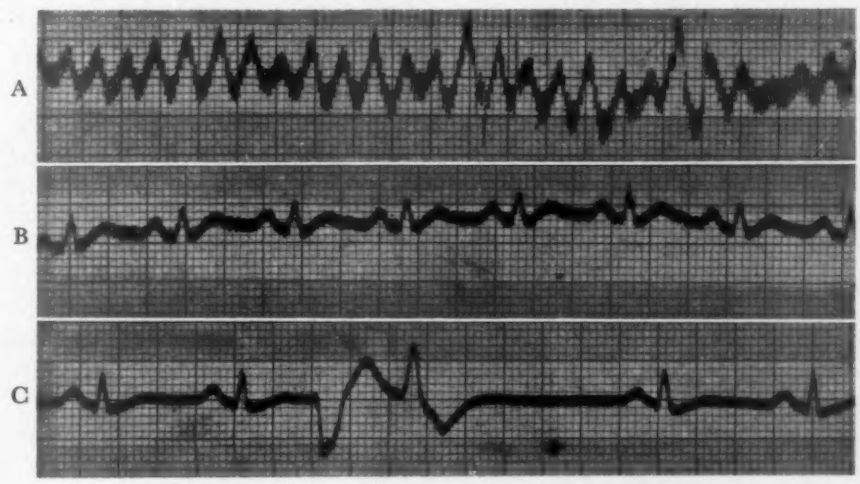


FIG. 4. A, recurrence of ventricular fibrillation. B, normal sinus rhythm immediately after third shock. C, multifocal ventricular premature beats.

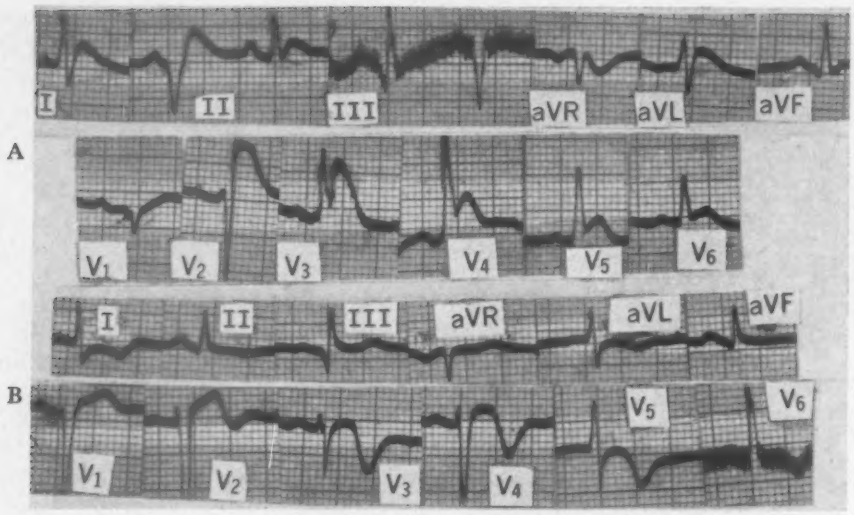


FIG. 5. A, taken one hour after Figure 4C. Increased injury pattern with isolated ventricular premature beats. B, taken eight hours after A, approximately twelve hours after Figure 1B. Injury pattern is decreased; tracing similar to that in Figure 1B.

plication of closed chest cardiac massage by a physician who happened to be in attendance at the moment of the cardiac catastrophe kept the circulation functioning until ventricular fibrillation could be proved by electrocardiogram. Immediate availability of a defibrillator made possible restoration of cardiac action after two electrical shocks. A third shock was necessary to abolish ventricular fibrillation which recurred ten minutes after the first successful defibrillation. Because of the prompt application of therapeutic measures, no brain damage ensued. Convalescence from the acute myocardial infarction proceeded without complications.

It is remarkable that several electric shocks apparently did no additional damage to the myocardium that could be detected by electrocardiogram, except for a brief period of increased injury pattern. The evolutionary changes on serial electrocardiograms did not differ appreciably from those usually seen in the course of an uncomplicated myocardial infarction.

Some aspects of the technic of closed chest cardiac massage appear to be of importance. In younger patients, in whom the chance of success are obviously more favorable in any event, the bony thorax is sufficiently elastic to withstand the trauma of the necessarily vigorous compression maneuvers. Fractures of ribs or sternum may occur in elderly or debilitated patients with demineralized bones. The compression of the thorax may provoke regurgitation of stomach contents, as occurred in our patient. Shock position and bronchial suction will prevent bronchial aspiration, thus averting complications that might jeopardize the life-saving effect of the cardiac massage. We also stress the importance of remembering, despite well-founded enthusiasm for this new advance in treatment, that the value of standard therapy (oxygen, vasopressor and antiarrhythmic drugs, etc.) has not been impaired.

SUMMARY

A forty-five year old patient suffered his second acute myocardial infarction and "died" suddenly. The presence of a physican during the catastrophe made possible immediate institution of closed chest cardiac massage, thus providing time for electrocardiographic diagnosis of ventricular fibrillation. Three defibrillator shocks restored normal sinus rhythm and the patient subsequently made an uncomplicated recovery.

ACKNOWLEDGMENT

We are indebted to Mr. Robert Hayes, senior technician of our electrocardiographic laboratory, for his assistance in preparing the tracings for this publication.

ADDENDUM

Since completion of this paper, house officers of our department succeeded in resuscitating another patient who had suffered an acute myocardial infarction.

On February 9, 1961, a fifty-two year old engineer was brought by car to our Emergency Room, complaining of pain in the joints of both arms, numbness in fingers and ill-defined dis-

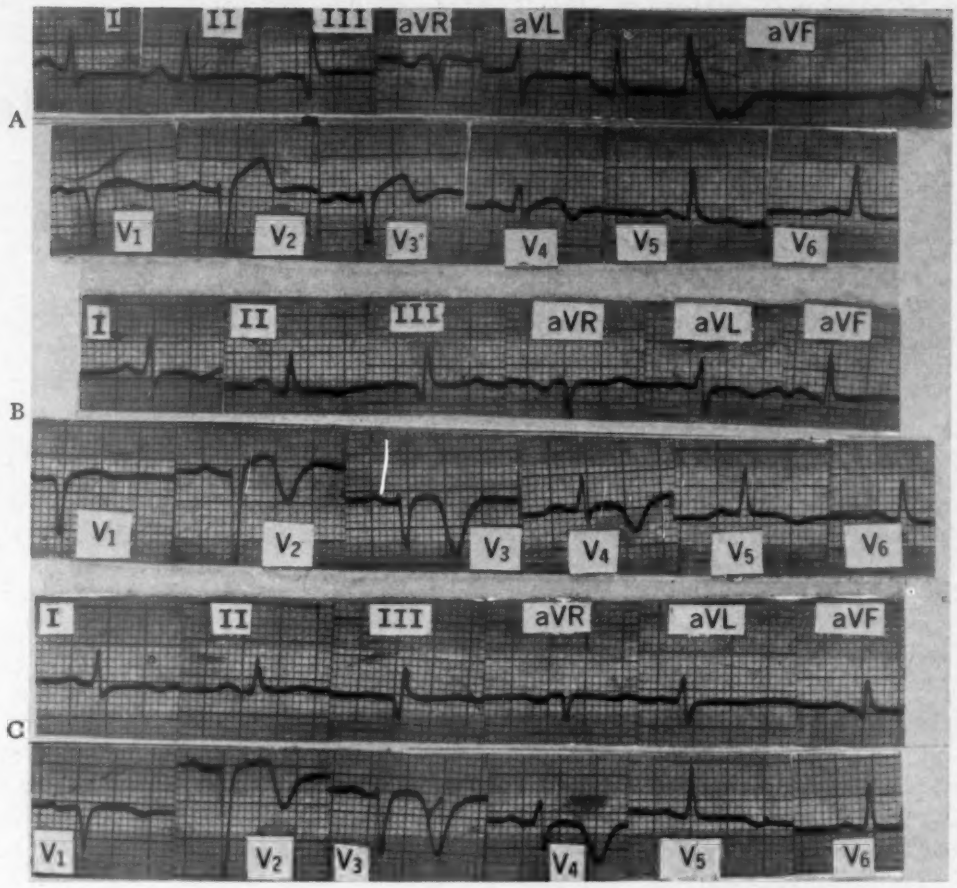


FIG. 6. A, December 9, 1960, four days after admission. Evolutionary changes. B, December 22, 1960, seventeen days after admission. Evolutionary changes. C, January 5, 1961, thirty-one days after admission. Evolutionary changes.

comfort in the chest. The electrocardiogram showed an acute anteroseptal myocardial infarction. Approximately thirty minutes after his arrival the patient had a tonic convulsion, he became cyanotic, his pupils dilated and pulse and respiration stopped. After initial blows to his chest by an attendant, closed chest cardiac massage and mouth to mouth breathing by two house officers were started within four to five minutes. Radial and femoral pulsations became palpable. Ventricular fibrillation was discovered on the electrocardiogram shortly thereafter. Two defibrillation shocks of 440 volts elicited a few sinus beats followed by the recurrence of ventricular fibrillation. Two defibrillation shocks of 880 volts converted this arrhythmia permanently to sinus rhythm. Antiarrhythmic drugs and pressor agents were subsequently needed and used as described above. The recovery was complicated by amaurosis of six hours' duration, retrograde amnesia of thirty-six hours' duration and a short-lasting recurrence of pain in the chest after four days. The patient was discharged on March 6, 1961.

REFERENCES

1. KOUWENHOVEN, W. B., JUDE, J. R. and KNICKERBOCKER, G. G. Closed chest cardiac massage. *J. A. M. A.*, 173: 1064, 1960.
2. SCHERF, D. and BORNEMANN, C. Thumping of the precordium in ventricular standstill. *Am. J. Cardiol.*, 5: 30, 1960.
3. ZOLL, P. M., LINENTHAL, A. J., GIBSON, W., PAUL, M. H. and NORMAN, L. R. Termination of ventricular fibrillation in man by externally applied electric countershock. *New England J. Med.*, 254: 727, 1956.

Cardiac Resuscitation after Documented Myocardial Infarction

Case Report of a "Successful Failure"*

DAVID J. TURELL, M.D.† *and* MAJ. ELIAS A. HUSNI, MC, USA‡
Fort Jackson, South Carolina

DURING THE PAST four years innumerable attempts have been made to resuscitate patients suffering cardiac arrest after myocardial infarction. To date only thirteen successful resuscitations with long term survival under these circumstances have appeared in the medical literature.[1–13] In all but three,[7,11,12] thoracotomy and cardiac massage were employed; of the three, one case of ventricular standstill responded to precordial thumping,[7] another to an external electrical pacemaker,[11] and a case of ventricular fibrillation was defibrillated externally.[12] In nine cases infarction was substantiated prior to cardiac arrest by characteristic electrocardiograms.[4–7,9–13]

The technics of cardiac massage and electric defibrillation are based chiefly upon the experimental work of Wiggers,[14,15] and were first applied successfully in the human being by Beck[16] in 1947. Successful resuscitation in the operating room has since become commonplace.[17,18] On the other hand, resuscitation after myocardial infarction usually takes place on the ward where the ideal circumstances of the operating room are completely wanting.

It is estimated that 100 cases of survivals with profound cerebral damage ("human vegetables"), requiring prolonged custodial care, occur each year in this country secondary to resuscitative attempts for cardiac arrest in the operating room.[19,20] Reports of this type of failure, following resuscitation for arrest secondary to acute myocardial infarction, have not yet appeared. Until the successful instances are compared with the failures, the true worth of these heroic and dramatic attempts will not be known. This case report represents such a "successful failure."

CASE REPORT

A forty year old white sergeant entered the U. S. Army Hospital at Fort Jackson, South Carolina, on June 17, 1959, complaining of a severe, dull, subxiphoid pain of three hours' duration. The pain radiated to both arms and was associated with a feeling of weakness. For several years the patient occasionally had experienced a vague substernal pressure sensation after exertion.

On physical examination the patient appeared pale and diaphoretic but not dyspneic. The blood pressure was 122/78 mm. Hg; the pulse was 82 beats per minute; respirations 20 per minute; and temperature 97.4 °F. The veins of the neck were not distended while the patient was supine. The lungs were clear to auscultation. Examination of the heart disclosed a systolic gallop rhythm at the apex, otherwise the sounds were of good quality. There were no enlarged organs, masses or tenderness in the abdomen. The peripheral pulses were within normal limits and the extremities were free of edema.

An electrocardiogram (Fig. 1) showed a pattern consistent with a very early acute anteroseptal myocardial infarction.

Resuscitation: The patient was placed in an oxygen tent and given morphine sulfate, 15 mg. intramuscularly. An hour later (11:25 A.M.) he was noted to be resting comfortably. At 11:35 A.M. the patient was discovered to be cyanotic and gasping; the ward physician was called and arrived at the bedside within one minute. No pulse was palpated and the heart beat was not audible. Precordial pounding and intracardiac injection of aqueous adrenalin (1 cc. of 1:1,000 solution) were employed, without apparent response, while a scalpel was obtained. Mouth to mouth breathing was instituted and a

* From the Departments of Medicine and Surgery, U. S. Army Hospital, Fort Jackson, South Carolina.
† Present address: Baylor University College of Medicine, Houston, Texas.
‡ Present address: Walter Reed Army Medical Center, Washington, D. C.

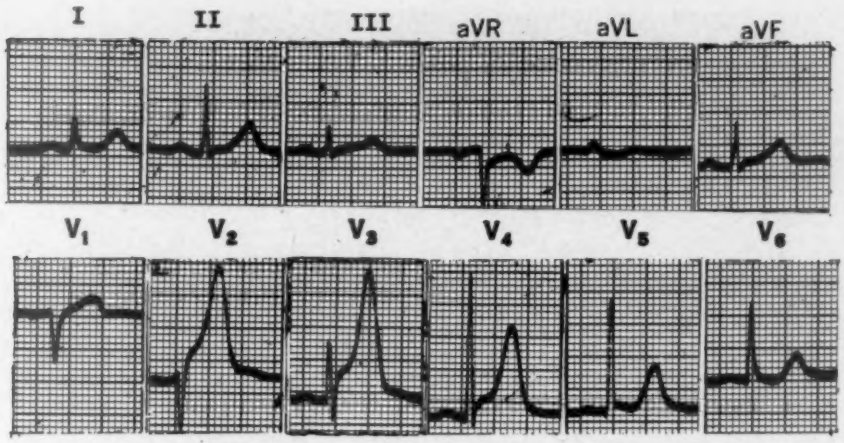


FIG. 1. Electrocardiogram taken a half hour after admission on June 17, 1959, showing very early changes of an acute anteroseptal myocardial infarction.

thoractomy was performed through the left fifth intercostal space. The heart was at standstill. Manual massage was begun; the lapse of time between arrest and massage was estimated to be four to six minutes. Within two minutes a vigorous ventricular fibrillation began, myocardial tone improved and well oxygenated blood oozed from the incision. The surgeon opened the pericardial sac and continued the massage. A 3 by 5 cm. area of purplish discoloration was observed on the anterior surface of the left ventricle. An endotracheal tube was inserted and the patient was oxygenated manually. Calcium gluconate 10 cc. (10 per cent solution) and 1 cc. of 1:1,000 aqueous adrenalin were injected into the left ventricle. Lanatoside C, 1.6 mg., was given intravenously. Electric defibrillation with a current of 70 volts was attempted four times before a persisting idioventricular rhythm returned. Intravenous atropine, 2 mg., was administered and within ten minutes a sinus rhythm with first degree atrioventricular block appeared. With the aid of l-norepinephrine a satifactory blood pressure was maintained and the patient was transferred to the operating room where the incisions were cleansed and closed under sterile conditions. Two million units of crystalline penicillin were instilled in the left pleural cavity.

Immediate Postoperative Course: After the chest was closed weak spontaneous breathing appeared. An intermittent positive pressure mask was employed to assist the patient for the first twenty-four hours. The rectal temperature was 103.4°F during the first night. Thereafter, it averaged 102°F for five days and then varied between 100 and 101°F. Penicillin and streptomycin were given for one week and then discontinued without alteration of the clinical course. There was no evidence of intrathoracic infection and the incision in the chest healed without complication. Follow-up electrocardiograms (Fig. 2) demonstrated an anteroseptal myocardial infarction with persistent S-T segment elevation. Administration of digitalis was continued. Anticoagulant therapy was started the first day but was discontinued after one week when profuse urinary bleeding occurred secondary to an indwelling catheter.

The patient was unresponsive for the first forty-eight hours. Babinski responses were present bilaterally, pupils remained small and fixed, corneal reflexes were absent and mild bilateral extensor spasticity of the legs and arms was noted during this period. After forty-eight hours the corneal and pupillary reflexes returned. The patient followed the ward personnel with his eyes and on one occasion he attempted to talk. Five days after the cardiac arrest the Babinski responses were gone and the patient began to look toward sounds and to move his head and arms when stimulated. Spasticity diminished and there was progressively greater mobility of arms and legs. By the end of a month he was able to eat soft food when fed and sit with assistance. He gave appropriate one word answers to simple

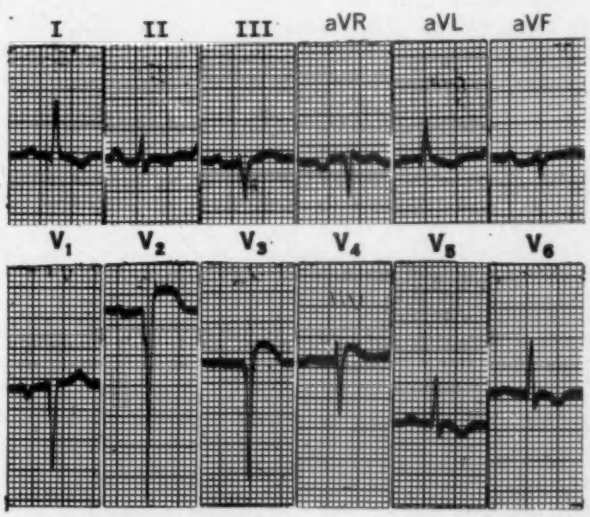


FIG. 2. Electrocardiogram taken July 7, 1959, three weeks after admission, demonstrating an anteroseptal myocardial infarction with ST-T changes compatible with digitalis effect.

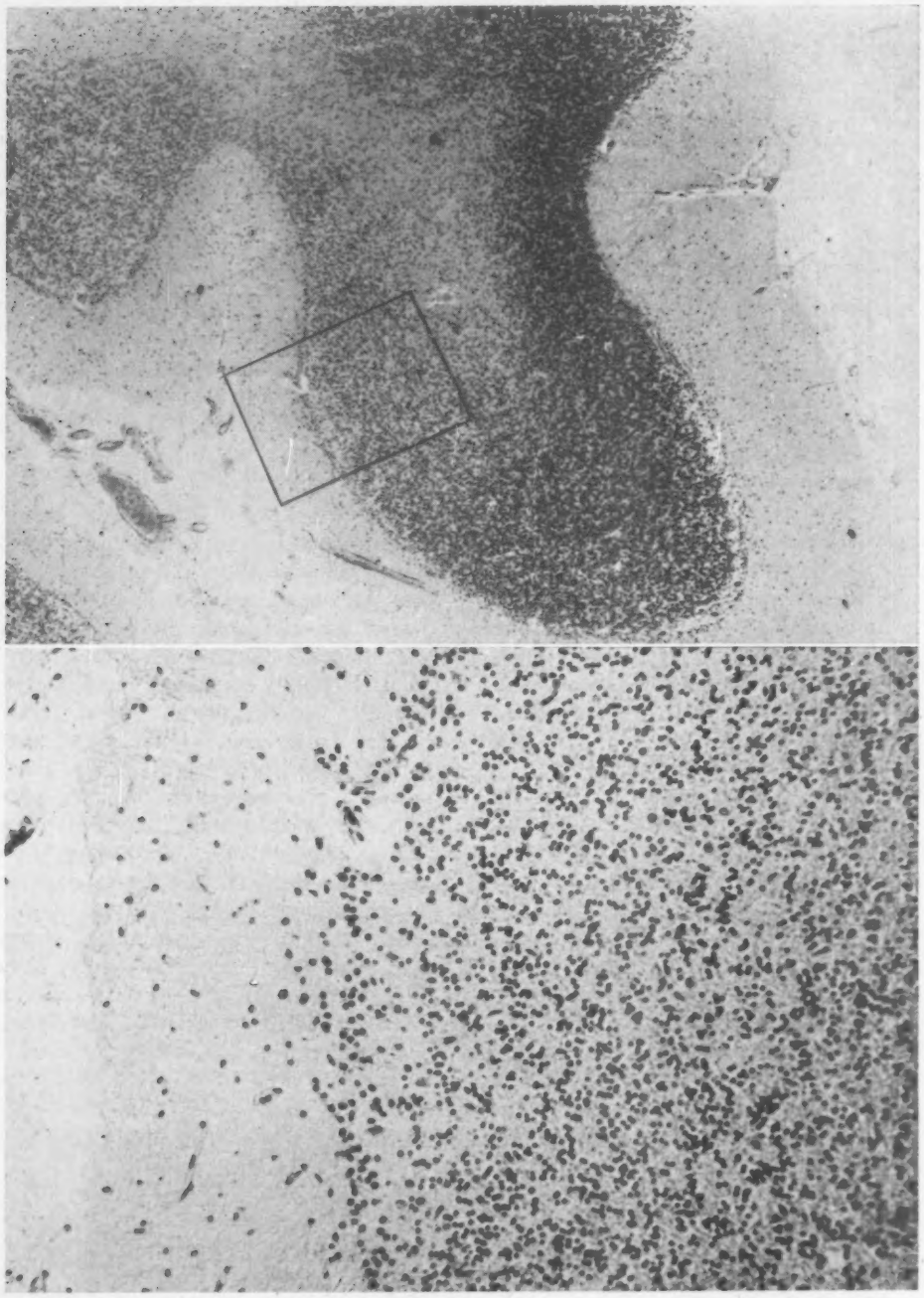


Fig. 3. Low power view (original magnification ×45) of cerebellum showing the thinning of the molecular layer, loss of Purkinje cells and decreased cellularity of the granular layer, particularly evident to the left.

Fig. 4. High power view (original magnification ×205) of the more severely involved area shown in Figure 3.

questions on several occasions and appeared to recognize his wife at least once. At this time a neuropsychiatric consultant believed that the vegetative nervous system was functioning adequately but that no consistent degree of intellectual function had been regained.

Subsequent Course: On July 15, 1959, the patient was transferred to Walter Reed Army Hospital for further rehabilitative care. The following day, signs of acute arterial occlusion of both legs developed, thought to be the result of embolization from left ventricular mural thrombi. The patient's general condition deteriorated further as his temperature rose to 103° F. The right lower leg became gangrenous and an amputation was performed above the knee. The patient became much less responsive

during this episode and it was believed that rehabilitation was no longer possible.

On September 17, 1959 the patient was transferred to the Veterans Hospital in Columbia, South Carolina for custodial care. He remained essentially comatose and despite meticulous care on a Strykker Frame numerous decubitus ulcers and an infection of the urinary tract developed. Septicemia, caused by a hemolytic Staphylococcus aureus, coagulase positive, obtained by blood culture, was thought to represent the primary cause of death on November 2, 1959.

POSTMORTEM FINDINGS

Autopsy examination* revealed the pericardial cavity to be obliterated approximately 50 per cent by fibrous adhesions. The heart weighed 400 gm. An anteroseptal myocardial infarction with marked thinning of the lower anterior left ventricular wall was present. There were no mural thrombi. There was moderate generalized coronary atherosclerosis with a thrombotic occlusion of the left anterior descending artery 4 cm. from its origin. There was patchy atelectosis of the lower lobes of both lungs with areas of chronic pneumonitis. Both spleen and kidneys contained old and recent embolic infarctions. Hydronephrosis and pyelonephritis of the right kidney was noted. The liver was unremarkable.

The brain weighed 1,220 gm. and after fixation the gross sections did not appear abnormal. However, microscopic examination demonstrated focal disappearance of nerve cells of the occipital cortex. Sections from the parietal and frontal lobes were normal. There was marked destruction in the cerebellum (Fig. 3 and 4): most Purkinje cells had disappeared, there was slight increase in cells of the Bergmann layer, several of the folia showed advanced granule cell rarefaction and astroglia in the granular layer had multiplied. Sections of the basal ganglia, midbrain, pons and medulla oblongata were essentially normal.

COMMENTS

It is now well recognized that "electrical failure" which occurs during myocardial infarction may be reversed by an alert physician, thus restoring an adequate rhythm for a patient who otherwise would have died.[1–13] It is apparent also that successful resuscitation includes more than restoration of the electrical system. First, the myocardium must be capable of responding to a reestablished rhythm with a cardiac output supportive of life. In this case the myocardial output was adequate. Second, resuscitative measures must re-establish oxygenation of the central nervous system usually within four minutes if permanent brain damage is to be avoided.[19–22] Although resuscitative measures were begun as expeditiously as circumstances allowed in this case, the time limit for the patient was exceeded. As a result he suffered cortical and severe cerebellar damage, although some areas were spared. This pattern of brain damage differs from previous reports[21,23] since cerebral cortical changes were limited only to the occipital region and the basal ganglia were spared. Cerebellar destruction was similar to the findings of others but somewhat unusual in that the granular layer was more severely involved than might be expected in view of the sparing of cerebral regions usually more sensitive to oxygen lack.[23] This spotty destruction suggests that anoxic brain damage was in the earliest stages when resuscitation was begun.

Undoubtedly marked edema of the brain was present for several days after the resuscitation and may have contributed to the ultimate neurologic deficit.[21,22,24] To decrease cerebral edema the use of prolonged hypothermia[22,24] and of hypertonic intravenous solutions of urea[25] have been recommended. Although neither therapy was employed in this case, the preliminary reports are encouraging and it is believed that these methods deserve a trial if cortical recovery is not noted within six to twelve hours after the resuscitation, or if signs of progressive damage appear.

The failure to preserve cerebral function in this patient should not deter further attempts at resuscitation. Other case reports demonstrate that prompt massage is capable of restoring both cardiac function and retaining cerebral integrity. Prompt resuscitation is warranted when the past history of the patient indicates that the myocardium is likely to be responsive to such efforts; i.e., when congestive failure or maintenance of blood pressure have not been problems prior to the arrest and when the four minute limit has not been exceeded. This limit should not be considered inflexible because successful resuscitations in the four to six minute range have been reported.[12,19,20,26]

"Thoracotomy and massage" is not the only method of resuscitation. External defibrillators and pacemakers have been effective following acute infarction in treating arrest secondary to both ventricular fibrillation and standstill.[11,12] Precordial percussion[27] and intracardiac epineph-

* Autopsy was performed by E. S. Cardwell, Jr., M.D., Pathologist, V. A. Hospital, Columbia, South Carolina. Brain sections were reviewed by Webb Haymaker, M.D., Armed Forces Institute of Pathology, Washington, D. C.

rine have both been employed successfully in cases of standstill.[7,28] Recent studies have shown that the cause of cardiac arrest following myocardial infarction is more likely to be ventricular standstill than fibrillation.[28,29] When arrest occurs and the cause is unknown, it may be worthwhile to employ precordial percussion and intracardiac epinephrine while swift preparations are made for thoracotomy. These simple measures may be successful and thus avoid the trauma to cardiac muscle associated with cardiac massage.[30] This sequence of events was employed in the present case without delaying the onset of massage.

The mechanism of arrest in this case; i.e., ventricular standstill or fibrillation, is not known; an electrocardiogram was not obtained at the exact moment of conversion to the terminal rhythm.[28] Although the heart appeared to be in standstill at the onset of massage the atonic fourth stage of ventricular fibrillation, as described by Wiggers,[14] may have been present. Furthermore, the sudden appearance of vigorous ventricular fibrillation during massage is a common sequence of events[8,28,31,32] and may follow documented asystole.[28] Thus, it is impossible to determine the mechanism of death in this case, as well as in others, without electrocardiographic evidence.

Summary

A case report of successful resuscitation of a heart following arrest secondary to acute myocardial infarction is presented. Unfortunately, severe and permanent brain damage occurred, and the patient became a human "vegetable" requiring prolonged custodial care. Methods of possibly preventing such damage are discussed. The view is presented that resuscitation should be attempted when it is believed that the myocardium will be capable of an adequate response, and the risk of central nervous system damage should not deter the physician from the attempt. It is further suggested that percussion of the chest and intracardiac epinephrine may be employed prior to the use of massage if the mechanism of death is not known.

Addendum

Closed chest cardiac massage, recently developed at the School of Medicine of Johns Hopkins University and reported after preparation of this article, merits careful consideration. Of eleven patients with cardiac arrest following myocardial infarction, four were successfully resuscitated with an intact central nervous system.[33]

References

1. Reagan, L. B., Young, K. Y. and Nicholson, J. W. Ventricular defibrillation in patient with probable acute coronary occlusion. *Surgery*, 39: 482, 1956.
2. Beck, C. S., Weckesser, E. C. and Barry, F. M. Fatal heart attack and successful defibrillation: new concepts in coronary artery disease. *J. A. M. A.*, 161: 434, 1956.
3. Celio, A. Cardiac arrest associated with coronary occlusion: successful resuscitation. *J. Internat. Coll. Surgeons*, 25: 299, 1956.
4. Bloomfield, D. K. and Mannick, J. A. Successful resuscitation in acute myocardial infarction with ventricular fibrillation. *New England J. Med.*, 258: 1244, 1958.
5. McGregor, J. G. and Newton, D. E. The treatment of cardiac arrest following myocardial infarction. *U. S. Armed Forces Med. J.*, 10: 125, 1959.
6. Conklin, W. H., Beebe, R. T. and Frawley, T. F. Ventricular fibrillation due to myocardial infarction with survival. *Arch. Int. Med.*, 104: 281, 1959.
7. Brandenburg, J. T. Successful treatment by a chest blow of cardiac arrest during myocardial infarction. *J. A. M. A.*, 170: 1307, 1959.
8. Hannon, D. W., Brainard, J. B. and Flom, R. S. Resuscitation from cardiac arrest due to acute coronary thrombosis. *Dis. Chest*, 31: 655, 1957.
9. Nickel, S. N. and Gale, H. H. Altered prognosis with cardiac massage. Cardiac resuscitation in acute myocardial infarction. Report of two successfully treated cases. *J. A. M. A.*, 170: 23, 1959.
10. Mota, C., Zikria, E. A. and Taber, R. E. Cardiac arrest outside the operating room with successful resuscitation: report of two cases. *Ann. Int. Med.*, 51: 577, 1959.
11. Solarz, S. D., Berkson, D. M. and Pick, A. Asystole complicating acute myocardial infarction: survival with aid of cardiac pacemaker and intravenous administration of isoproterenol. *J. A. M. A.*, 168: 2124, 1958.
12. Nast, P. R., Pennypacker, C. S. and Wagner, J. A. Successful external electrical defibrillation in acute myocardial infarction. Report of a case. *Circulation*, 22: 138, 1960.
13. Walton, R. S. Cardiac massage for cardiac arrest following coronary thrombosis. *Brit. Med. J.*, 5167: 155, 1960.
14. Wiggers, C. J. The mechanism and nature of ventricular fibrillation. *Am. Heart J.*, 20: 399, 1940.
15. Wiggers, C. J. The physiologic basis for cardiac resuscitation from ventricular fibrillation. Method for serial defibrillation. *Am. Heart J.*, 20: 413, 1940.
16. Beck, C. S., Pritchard, W. H. and Feil, H. S. Ventricular fibrillation of long duration abolished by electric shock. *J. A. M. A.*, 135: 985, 1947.
17. Hinton, J. W., Stephenson, H. E. and del Missier, P. A. Cardiac arrest: a resume of experimental and clinical data. *J. Nat. Med. Assoc.*, 49: 11, 1957.
18. Singleton, H. O., Jr. and DeLoach, A. W. Cardiac arrest. *Texas Reports Bio. & Med.*, 13: 1027, 1955.

19. Cole, S. L. and Corday, E. Four minute limit for cardiac resuscitation. *J. A. M. A.*, 161: 1454, 1956.
20. Cole, S. L. and Corday, E. The internist and cardiac arrest. *Arch. Int. Med.*, 104: 37, 1959.
21. Mandel, M. M. and Berry, R. G. Human brain changes in cardiac arrest. *Surg. Gynec. & Obst.*, 108: 692, 1959.
22. Williams, G. R., Jr. and Spencer, F. C. The clinical use of hypothermia following cardiac arrest. *Ann. Surg.*, 148: 462, 1958.
23. Loken, A. C., Haymaker, W. and Paulson, D. L. Stab wound of the heart followed by temporary cessation of the heartbeat with resuscitation by cardiac massage. *Surgery*, 26: 745, 1949.
24. Benson, D. W., Williams, G. R., Jr., Spencer, F. C. and Yates, A. J. The use of hypothermia after cardiac arrest. *Anesth. & Analg.*, 38: 423, 1959.
25. Javid, M. Urea. New use of an old agent: Reduction of intracranial and intraocular pressure. *Surg. Clin. North America*, 38: 907, 1958.
26. Southworth, H. The resuscitation problem. *Circulation*, 20: 946, 1959.
27. Scherf, D. and Bornemann, C. Thumping of the precordium in ventricular standstill. *Am. J. Cardiol.*, 5: 30, 1960.
28. Hellerstein, H. K. and Turell, D. J. Mode of death in coronary artery disease; electrocardiographic and clinicopathologic correlation. In press.
29. Enselberg, C. D. The dying human heart. Electrocardiographic study of 43 cases with notes on resuscitative attempts. *Arch. Int. Med.*, 90: 15, 1952.
30. Adelson, L. Clinicopathologic study of anatomic changes in heart resulting from cardiac massage. *Surg. Gynec. & Obst.*, 104: 513, 1957.
31. Turk, L. N. III, and Glenn, W. W. L. Cardiac arrest. Results of attempted cardiac resuscitation in 42 cases. *New England J. Med.*, 251: 795, 1954.
32. Briggs, B. D., Sheldon, D. B. and Beecher, H. K. Cardiac arrest. Study of a 30 year period of operating room deaths at Massachusetts General Hospital, 1925–1954. *J. A. M. A.*, 160: 1439, 1956.
33. Kouwenhoven, W. B., Jude, J. R. and Knickerbocker, G. G. Heart activation in cardiac arrest. *Mod. Conc. Cardiovasc. Dis.*, 30: 639, 1961.

Successful Treatment of Ventricular Fibrillation with Intracardiac Potassium Chloride*

LEONARD WEINSTOCK, M.D.† *and* CAPT. JAMES H. CLARK, USAF(MC)

New York, New York

CARDIAC ARREST is a common medical emergency. Stephenson[1] estimates that between 7,500 to 9,000 cases occur in this country each year. Initially, most successful resuscitations were achieved in the operating rooms of large teaching centers. Recently, the scope of resuscitative success has expanded to include emergency rooms, x-ray departments, patients' rooms, physicians' offices and even areas outside the confines of the hospital.[2] Beck[3] has predicted that with properly trained personnel and readily available equipment, resuscitation will be carried out in the home or even on the golf course.

Under such conditions standard procedures may not be applicable and improvised methods may be necessary. The following case is an example of the use of intracardiac potassium chloride in the treatment of ventricular fibrillation in such a situation.

CASE REPORT

M. G. was a three year old white boy who was admitted to the 1604th USAF Hospital on January 31, 1959 for an elective herniorrhaphy. His past history and physical examination were within normal limits except for a left inguinal hernia. His preoperative hemogram, urinalysis and x-ray film of the chest were not remarkable.

On the day after admission he was premedicated with meperidine 15 mg. and scopolamine 0.15 mg. intramuscularly. Forty-five minutes later he was taken to the operating room and anesthetized with an ether-nitrous oxide-oxygen mixture. Both induction and maintenance were described as smooth and uneventful.

The repair proceeded without incident. Just prior to the insertion of a skin suture he became rigid and cyanotic while under very light anesthesia. Signs of laryngospasm and bronchospasm were evident, associated with extreme trismus. Endotracheal intubation was impossible under these conditions so an airway was maintained with a nasopharyngeal tube. Artificial respiration was initiated using a tight-fitting face mask and a manually compressed bag of 100 per cent oxygen. At this time the anesthetist reported that a heart beat was not obtainable. The surgeon struck several hard blows to the precordium without any effect. He then opened the chest through the fourth intercostal space. The heart appeared dilated in standstill; however, after several compressions it assumed the vermiform pattern of ventricular fibrillation. It is estimated that approximately three minutes elapsed between the recognition of the catastrophe and the initiation of effective cardiac output by massage.

After several minutes of massage, 5 cc. of 0.5 per cent procaine was injected into a ventricle with the abolition of the ventricular fibrillation. It cannot be stated with certainty into which ventricle the solution was injected. Massage was continued for several minutes without any detectable spontaneous beat. Therefore, 2 cc. of epinephrine, 1:100,000 solution, was injected into the ventricle with prompt re-establishment of fibrillation. A second dose of 5 cc. of procaine was then injected without effect. Shortly thereafter, 5 cc. of 10 per cent calcium gluconate was injected also without effect.

By this time an electrocardiograph was available and a tracing confirmed the presence of ventricular fibrillation (Fig. 1A). An extension cord was cut across and the uninsulated ends wrapped about a pair of clamps. These were placed on either side of the heart and three successive shocks were applied by quickly inserting and withdrawing the plug from the wall socket. This produced a searing effect on the heart muscle but no change in its electrical activity.

Two cubic centimeters of potassium chloride (2 mEq. per cc.) was then injected into the ventricle

* From the 1604th USAF Hospital, APO 856, New York, New York.

† Present address: Department of Medicine, The Mount Sinai Hospital, New York, New York.

with transient standstill and prompt escape to a slow flutter-fibrillation pattern (Fig. 1B). A second 2 cc. dose of potassium chloride produced cardiac standstill (Fig. 1C). Massage was continued for thirty to forty seconds when suddenly the heart resumed a spontaneous beat. Electrocardiograms revealed a slow idioventricular rhythm which gradually accelerated and spontaneously converted to sinus rhythm (Fig. 1D–G). At this time the patient's pupils became reactive and strong and unassisted respirations occurred. It is estimated that his cardiac output had been maintained for thirty-five minutes by cardiac massage.

The chest wound was closed and an underwater drainage tube left in place. The herniorrhaphy wound was closed and the patient carefully observed for the next few hours on the operating table.

Postoperative Course: For the first six hours he remained obtunded. His vital signs were stable. His pupils were dilated but reacted slowly to light. There was a decerebrate response to pain with opisthotonus and extensor rigidity.

By twelve hours postoperatively he began making purposeful movements, opened his eyes to name-calling and withdrew from painful stimuli. His x-ray film of the chest showed full re-expansion of the left lung and the electrocardiogram was not remarkable except for S-T elevation in the precordial leads and sinus tachycardia.

By twenty-four hours postoperatively the patient was fully conscious, able to converse with his parents in his usual fashion and showed no detectable memory loss. At this time there was, however, serious question about his vision. It was noted that he would not follow a light or react to colorful objects. The fundi revealed scattered flame-shaped hemorrhages throughout.

On the third postoperative day the chest tube was removed. However, an x-ray film of the chest revealed a 2 cm. bulge along the left cardiac border. Fluoroscopy confirmed the presence of a 2 to 3 cm. bulge on the posterolateral wall of the left ventricle which showed paradoxical pulsation. At this time his electrocardiogram was entirely normal.

His subsequent course was one of steady improvement. He began to follow light, played with familiar colored objects and walked without difficulty. Repeat x-ray and fluoroscopic examination one week later did not reveal the aneurysmal area. He was, therefore, discharged on the thirteenth hospital day.

A follow-up letter from the child's parents, one year later, states that he appears to be normal in all respects. Medical confirmation of this is not available at this time.

Comments

Ventricular fibrillation occurs much less frequently than cardiac standstill. Of the 1,710 cases of arrest in the Cardiac Arrest Registry in 1958, 11.3 per cent were caused by fibrillation.[4] Ventricular fibrillation has also been produced by massage of an anoxic arrested heart[5] as occurred in our case. It is almost universally accepted that *electrical countershock* is the procedure of choice for defibrillation. Current flows of 1.5 to 3 amperes are needed to defibrillate the human heart.[6] Defibrillation units which can supply these currents in a safe, reliable manner are now commercially available and in wide usage.

In our case such a unit was not available and an attempt was made to improvise an electrical

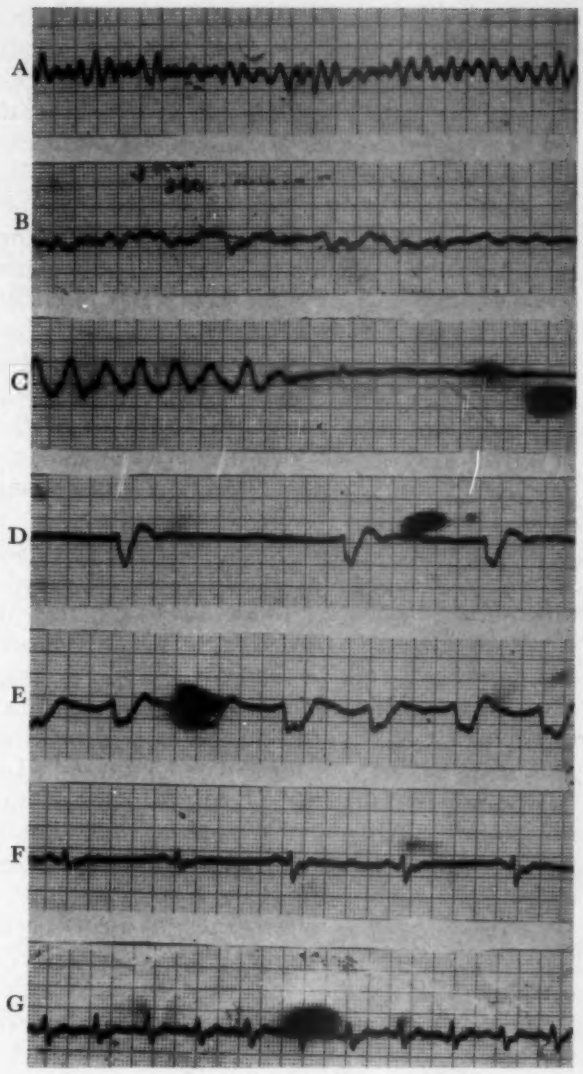


Fig. 1. A, ventricular fibrillation. B, injection of 2 cc. potassium chloride (300 mg.) with transient standstill. C, recurrence of flutter-fibrillation (thirty seconds later) with complete arrest following second injection of 2 cc. of potassium chloride (300 mg.). D, irregular idioventricular beats following cardiac massage. E, idioventricular rhythm. F, sinus rhythm with intraventricular conduction defect. G, sinus tachycardia.

countershock unit using a lamp fixture cord and wall socket. MacKay[7] reported a personal communication by Mooslin of a successful defibrillation using an identical makeshift unit. Our efforts produced only superficial electrical burns without effect upon the arrhythmia. Analysis of the system readily indicates the cause of failure. MacKay[6] showed that the inherent resistance of the canine heart is 45 to 60 ohms and 85 to 170 volts are needed to safely defibrillate. Our line voltage supplied only 110 volts. If one considers the inherent resistance of the human heart (46 to 93 ohms), the pericardium, the small area of the electrodes and poor insulation, it is easy to see why the flow of current was ineffective and produced only a searing effect.

The first drug used was *intracardiac procaine.* A number of cases have been reported in which procaine or procaine amide have either converted fibrillation or made the refractory heart again responsive to electric countershock. Some investigators believe its use is dangerous because the inherent rhythm of the heart is depressed and sinus rhythm is difficult to initiate.[8] In our case such did occur; procaine abolished the fibrillation but a spontaneous rhythm could not be established and fibrillation recurred following stimulation by epinephrine.

Potassium arrest of a fibrillating heart has been well documented exerimentally. Hooker[9] successfully defibrillated dogs with the coronary perfusion of potassium chloride and reinstituted sinus rhythm by perfusion of calcium chloride. Wiggers[10] in a series of experiments on dogs demonstrated that potassium chloride in a dose of 50 mg. per kg. injected into both ventricles produced standstill of electrically-induced fibrillation. By electrocardiograms and cinematography, he distinguished two types of fibrillation: (1) the faradic type which was faster at 300 to 600 cycles per minute, irregular and uncoordinated; and (2) a potassium-induced type which was slower at 150 to 270 cycles per minute, regular and undulating. In our case, 300 mg. (20 mg. per kg.) of potassium chloride was initially injected into the left ventricle, producing almost immediate standstill (Fig. 1B). This was promptly followed by a slower, regular flutter fibrillation (Fig. 1C) similar to that described by Wiggers. Following the injection of an additional 300 mg., making a total of 40 mg. per kg., complete standstill was produced.

Kolff, Effler and co-workers[11] applied to human subjects the potassium perfusion technic of Melrose[12] to produce successful elective cardiac arrest in open heart surgery. Standstill was produced within a few seconds of the injection. Recovery of a spontaneous heart beat occurred, usually within the first minute of perfusion with the patient's blood. Ventricular fibrillation developed in several of their cases in the recovery phase and these were either reperfused with potassium citrate or defibrillated by electric countershock. These authors indicated that potassium appeared more effective in arresting recurrent fibrillation. In only one case out of thirty-seven was it impossible to initiate a spontaneous heart beat.

Potassium chloride arrest was successfully used by Craft et al.[13] in a case of "spontaneous" ventricular fibrillation. Fibrillation developed in a severely burned man, while he was undergoing skin grafting. Cardiac massage was initiated promptly and maintained for approximately fifteen minutes until 20 mEq. of potassium chloride (27 mg. per kg.) were injected into the left ventricle. Standstill occurred promptly and massage was maintained. Sinus rhythm appeared within three minutes and the patient made a full uneventful recovery.

In these few cases initiation of a spontaneous heart beat offered no particular problem. It usually occurred within a few minutes of injection while massage was being continued. Presumably, this served to lower the local hyperkalemia to levels at which a spontaneous rhythm could occur. It has been demonstrated experimentally that drugs which lower serum potassium levels will shorten the recovery phase in potassium-induced arrest. Both hypertonic glucose and insulin[14] and 10 per cent sodium lactate[15] have proved effective and could possibly be used in refractory cases.

The calcium ion has been shown to have an antagonistic action to potassium on the myocardium. Both Hooker[9] and Wiggers[10] used calcium chloride to reinstitute sinus rhythm after potassium-induced standstill. Kay and Blalock[16] found 10 per cent calcium chloride effective in four cases of cardiac arrest. However, Melrose and his associates believed that although both calcium chloride and epinephrine restored muscle tone, they frequently induced ventricular fibrillation.[17] In our case epinephrine appeared to have induced a rather refractory fibrillation following procaine-induced arrest.

Our patient had an aneurysmal bulge on the wall of the left ventricle. It is postulated that

this represented an area of contusion produced by overzealous massage. An analysis of sixty autopsied cases following cardiac massage revealed moderate to severe contusion in almost 50 per cent with frank laceration in six.[18] These changes seemed to be more closely related to technic of massage than to its duration. In our case the damaged area was not detectable one week later and did not appear to be of clinical importance.

Summary

A case is reported of ventricular fibrillation occurring during herniorrhaphy and successfully treated with intracardiac potassium chloride and cardiac massage.

Acknowledgment

We are deeply indebted to Drs. William C. Johnson, Fred G. Smith and Capt. Clarabel Nelson for their aid and assistance in this crisis. We also wish to thank Dr. Leslie A. Kuhn for reviewing our manuscript.

References

1. Stephenson, H. E. Cardiac Arrest and Resuscitation, p. 32. St. Louis, 1958. C. V. Mosby.
2. Stephenson, H. E. Reference 1, pp. 39–42.
3. Beck, C. S., Weckesser, E. C. and Barry, F. M. Fatal heart attack and successful defibrillation. *J. A. M. A.*, 161: 434, 1956.
4. Stephenson, H. E. Reference 1, p. 52.
5. Johnson, J. and Kirby, C. K. The surgical treatment of ventricular fibrillation. *Ann. Surg.*, 134: 672, 1951.
6. MacKay, R. S., Mooslin, K. E. and Leeds, S. The effects of electric currents on the canine heart with particular reference to ventricular fibrillation. *Ann. Surg.*, 134: 173, 1951.
7. MacKay, R. S. Ventricular defibrillators. *J. A. M. A.*, 154: 1421, 1954.
8. Stephenson, H. E. Reference 1, pp. 179–180.
9. Hooker, D. R. On recovery of the heart in electric shock. *Am. J. Physiol.*, 91: 305, 1930.
10. Wiggers, C. Studies of ventricular fibrillation produced by electric shock. *Am. J. Physiol.*, 93: 197, 1930.
11. Kolff, W. J., Effler, D. B., Grover, L. K. and Moraca, P. P. Elective cardiac arrest with potassium citrate during open heart operations. *J. A. M. A.*, 164: 1653, 1957.
12. Melrose, D. G., Dreyer, B., Bentall, H. H. and Baker, J. B. E. Elective cardiac arrest. *Lancet*, 269: 21, 1955.
13. Craft, J. W., McCormack, R. M. and Dale, W. A. Treatment of ventricular fibrillation with potassium chloride: successful resuscitation in a severely burned patient. *Plastic & Recon. Surg.*, 20: 437, 1957.
14. Mavor, G. E., McEvoy, R. K. and Maloney, E. B. The effectiveness of hypertonic glucose in the resuscitation of hypothermic heart following potassium chloride arrest. *Circulation Res.*, 4: 389, 1956.
15. Schimert, G. and Cowley, R. A. Defibrillation, cardiac arrest and resuscitation in deep hypothermia by electrolyte solutions. *Surgery*, 41: 211, 1957.
16. Kay, J. H. and Blalock, A. The use of calcium chloride in the treatment of cardiac arrest in patients. *Surg., Gynec. & Obst.*, 92: 97, 1951.
17. Stephenson, H. E. Reference 1, pp. 294–295.
18. Adelson, L. A. Clinico-pathologic study of the anatomic changes in the heart resulting from cardiac massage. *Surg., Gynec. & Obst.*, 104: 513, 1957.

Use of Isoproterenol in the Treatment of Complete Heart Block Complicating Acute Myocardial Infarction*

JOHN H. K. VOGEL, M.D.†
Nashville, Tennessee

TEN TO NINETEEN PER CENT of all cases of complete heart block result from acute myocardial infarction; heart block is observed in 1 to 3 per cent of patients with acute myocardial infarction.[1-6] Treatment is often unsatisfactory as evidenced by the reported mortality rates of 43 to 100 per cent.[3-6] This paper reports a case of acute myocardial infarction complicated by heart failure, shock and complete heart block successfully treated with the continuous intravenous administration of isoproterenol.

CASE REPORT

A. B., fifty-six year old white married man, was admitted to Thayer Veterans Administration Hospital, Nashville, Tennessee, on July 27, 1958, with the chief complaint of nausea, vomiting and pain in the chest of ten hours' duration. He had been in good health until ten months prior to admission when he noted the onset of epigastric pain with retrosternal radiation and occasional nausea and vomiting. On the day of admission the patient experienced an unusually severe episode of pain in the chest radiating into both arms and neck and accompanied by persistent nausea and vomiting.

Physical Examination: The patient was an acutely ill, moderately obese white man who complained of severe pain in the chest. The oral temperature was 99.2°F., the pulse rate was 70 beats per minute and regular, respirations were 20 per minute and the blood pressure was 130/70 mm. Hg. The skin was cool and clammy. Arcus senilis was prominent. The neck veins were flat. The anteroposterior diameter of the chest was increased and breath sounds were decreased throughout. No rales were heard. The left border of cardiac dullness was at the midclavicular line and the precordium was quiet. The heart sounds were of poor quality; a gallop and loud pericardial friction rub were heard.

Laboratory Studies: The white blood cell count was 9,000 cells per cu. mm. on admission and rose to 13,500 on the second day. The hematocrit was 38 per cent. Blood urea nitrogen, serum cholesterol and fasting blood sugar were within normal limits. Serum glutamic oxalacetic transaminase was 45 units at six hours, 130 units at twenty-four hours and 95 units at forty-eight hours. The electrocardiogram revealed changes suggestive of an acute inferior wall myocardial infarction (Fig. 1A). The initial prothrombin time was 74 per cent of normal and with two exceptions was subsequently maintained between 10 and 30 per cent of normal with bishydroxycoumarin.

Hospital Course: The patient was treated with bedrest, sedation, nasal oxygen, anticoagulants and large doses of narcotics to control the pain. On the second day a first degree heart block was noted (Fig. 1B). On the third hospital day a 2:1 A-V block developed with a decrease in the pulse rate to 45 per minute (Fig. 1C). The blood pressure remained stable and the pericardial friction rub disappeared. On the fourth day there was a further reduction in the pulse rate to 30 with the appearance of complete A-V block (Fig. 1D). The patient became disoriented and complained of increasingly severe dyspnea and pain in the chest. Physical examination revealed distention of the veins in the neck, rales in both lungs and an enlarged, tender liver. The patient received 1.5 mg. of digoxin over a period of eighteen hours with progressive improvement in his heart failure.

On the fifth hospital day there was a further decrease in the pulse rate to 12 associated with a fall in blood pressure to 70/50 mm. Hg. The patient became semicomatose, restless and appeared moribund. One hundred milligrams of hydrocortisone intravenously did not alter the heart rate. Subsequently, 0.02 mg. isoproterenol was injected intravenously over a period of sixteen seconds. The tracing taken during

* From the Vanderbilt University School of Medicine, Department of Medicine and Thayer Veterans Administration Hospital, Nashville, Tennessee.
† Present address: University of Colorado Medical Center, Denver, Colorado.

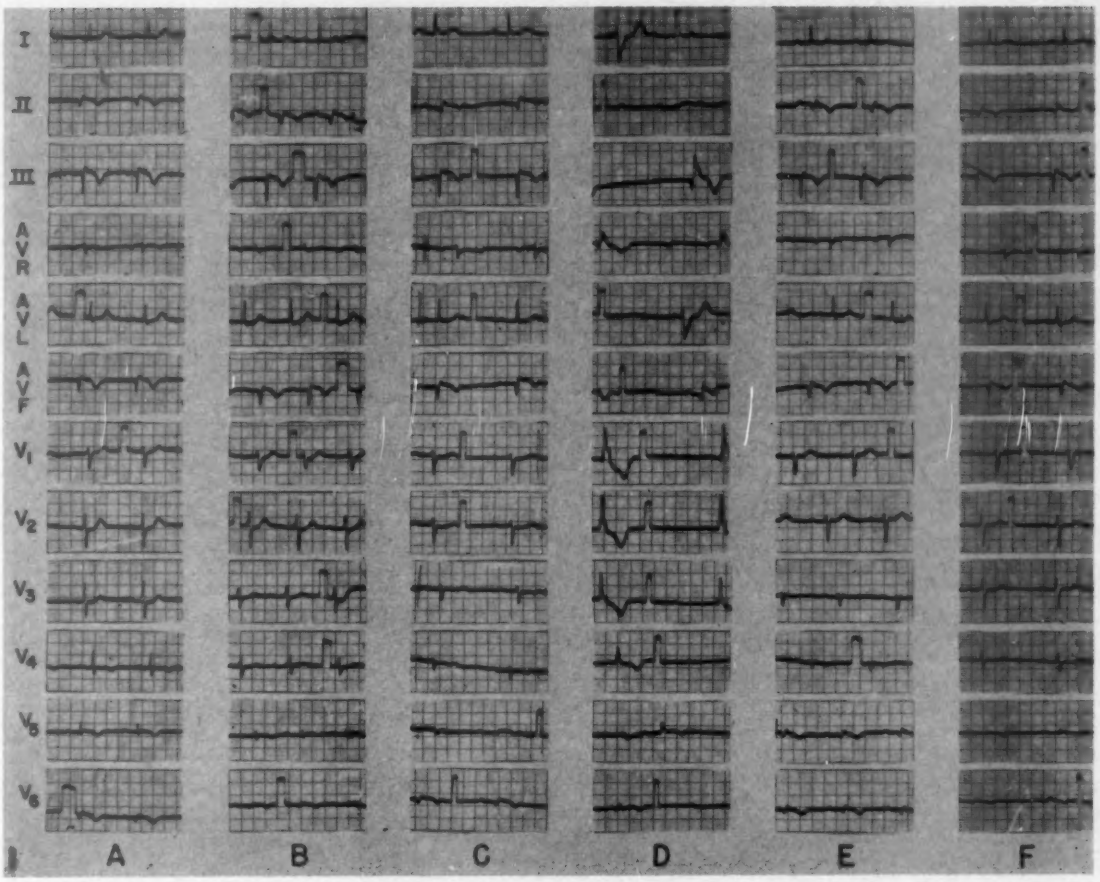


FIG. 1. Serial electrocardiograms. A, taken July 27, 1958; B, taken July 28, 1958, C, July 29, 1958; D, July 30, 1958, E, taken August 8, 1958; and F, January 1, 1959.

the administration of isoproterenol revealed an idioventricular pacemaker with rare conducted beats. Ten seconds after the injection of isoproterenol there was an increase in the atrial rate and in the number of conducted beats. Within sixty seconds there was complete suppression of the idioventricular pacemaker and a 2:1 A-V block had been established (Fig. 2). Ten minutes later slowing of the heart rate and runs of idioventricular beats were again noted. Following another intravenous injection of 0.01 mg. isoproterenol there was an increase in atrial rate and improved A-V conduction, with suppression of the idioventricular focus and establishment of a 2:1 A-V block (Fig. 3). The blood pressure returned to a normal level following the increase in heart rate.

The patient was then started on a continuous intravenous infusion of isoproterenol at a rate of 1.4 μg. per minute with maintenance of the pulse rate between 50 and 60 per minute and a blood pressure of 100/70 mm. Complete A-V block was present with the pacemaker in the atrioventricular node (Fig. 4A). By increasing the rate of the drip it was possible to reestablish a 2:1 A-V block. Daily attempts were made to discontinue the drip but each time there was slowing of the pulse rate with a fall in blood pressure. Four days after isoproterenol therapy was started, with an infusion rate of 1.4 μg. per minute, there was a spontaneous change to sinus rhythm and first degree heart block (Fig. 4B). Again, following the reversion to sinus rhythm repeated attempts were made to discontinue isoproterenol. On each occasion within ten to fifteen minutes after stopping the isoproterenol there was reversion to second and third degree heart block with a slowing rate (Fig. 4C and E). However, sinus rhythm was easily maintained with decreasing amounts of isoproterenol until an infusion rate of 0.4 μg. per minute was reached on the ninth day. The sinus rhythm was maintained for the first time when the drug was discontinued (Fig. 4G). Thirty minutes after isoproterenol had been discontinued there was an increase in the P-R interval from 0.24 to 0.28 second and a decrease in the pulse rate to 48. However, during the next ten hours there was a gradual increase in the pulse rate to 65 and decrease in the P-R interval to 0.24 second (Fig. 1E). The first degree heart block persisted throughout the hospital stay, although the P-R interval had decreased to 0.21 second on the day of discharge.

The patient received several injections of 0.4 mg. atropine for his nausea before and during the administration of isoproterenol and at no time was there any

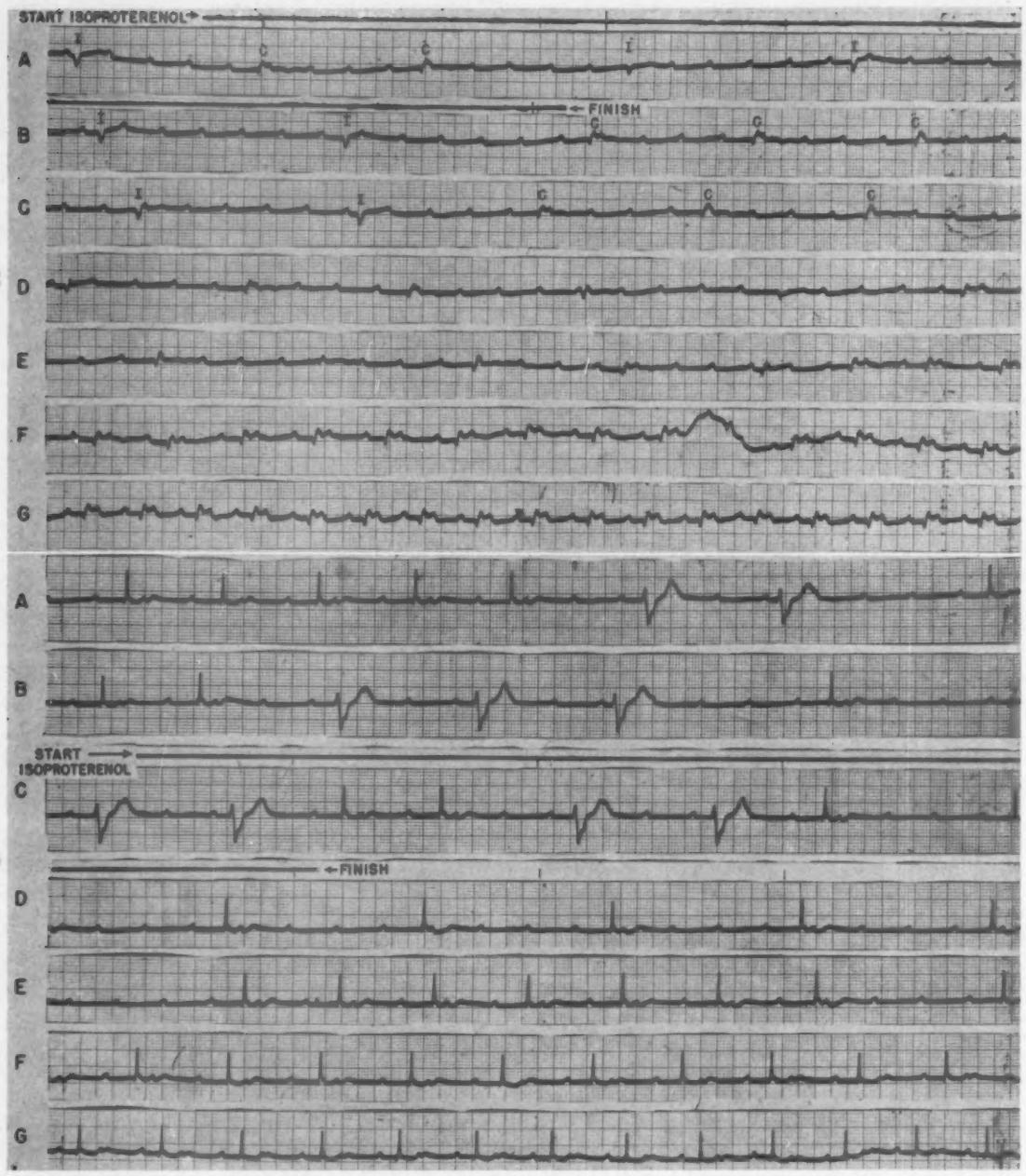


FIG. 2. Lead II. Continuous tracing during and following intravenous administration of 0.02 mg. isoproterenol. See text for explanation. I = idioventricular; C = conducted.

FIG. 3. Lead I. Continuous tracing during and following the intravenous administration of 0.01 mg. isoproterenol. See text for explanation.

effect upon the pulse rate. The patient remained extremely disoriented, combative and hyperactive for three to four days after the acute episode of ventricular slowing. Five days after isoproterenol was started the patient demonstrated some improvement in his mental status and was able to take food satisfactorily. The hospital course is summarized in Figure 5. His last electrocardiogram taken six months after his original admission revealed persistence of the first degree heart block and residual signs of the inferolateral wall myocardial infarction (Fig. 1F). He has remained well compensated with digoxin 0.25 mg. daily and there has been no return of the complete heart block.

COMMENTS

The effect of acute complete heart block on cardiovascular hemodynamics of dogs has been studied by Starzl, Gaertner and Baker.[7,8] These investigators observed a decrease in heart rate, cardiac output, coronary blood flow, left

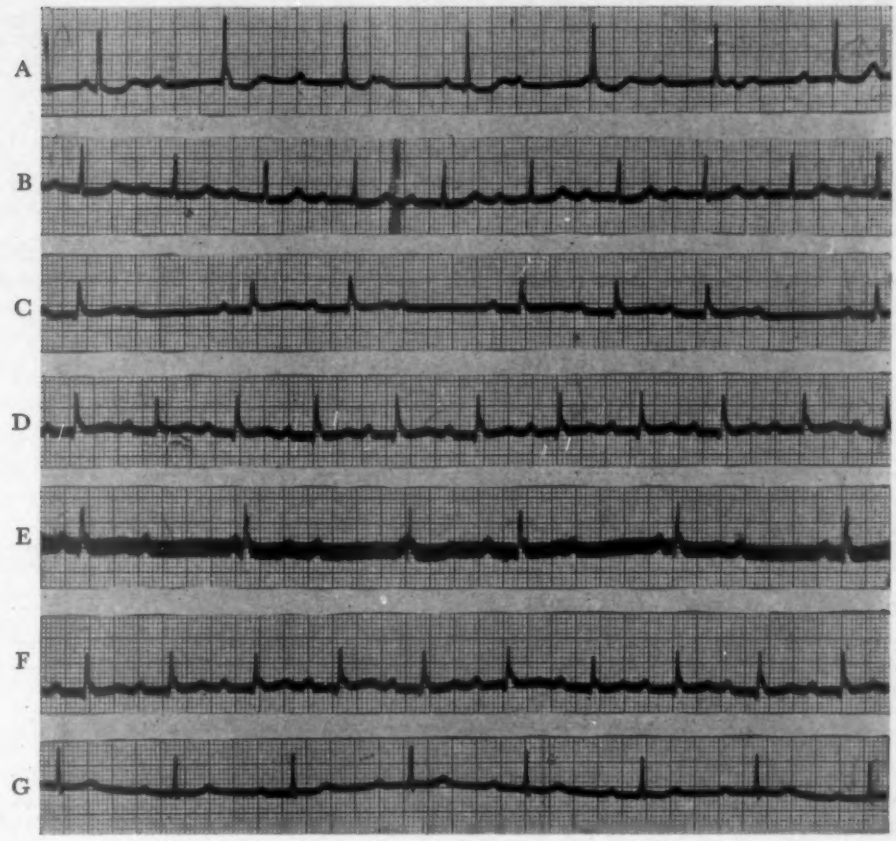


FIG. 4. A, complete A-V block during the second day while receiving isoproterenol intravenously at a rate of 1.4 μg. per minute. B, appearance of sinus rhythm with first degree heart block on the fifth day while receiving 1.4 μg. per minute of the drug. C, appearance of partial heart block with Wenckebach rhythm on fifth day, ten minutes after isoproterenol was discontinued. D, sinus rhythm with first degree heart block on sixth day with infusion rate of 0.7 μg. per minute. E, appearance of second and third degree heart block ten minutes after isoproterenol was discontinued on the sixth day. F, rapid reversion to sinus rhythm with first degree heart block one minute after drug was restarted on sixth day. G, persistence of first degree heart block after drug was discontinued on the ninth day.

ventricular work and mean arterial blood pressure and an increase in arteriovenous oxygen difference, stroke volume and right atrial pressure. No significant change in myocardial efficiency or oxygen consumption was noted. Similar changes have been noted in man by Chandler and Clapper[24] and Stack et al.[9] The effectiveness of isoproterenol in re-establishing normal hemodynamics in complete heart block has been well demonstrated. Following the administration of isoproterenol there is a positive inotropic effect with an increase in atrial and ventricular pacemaker rates, improved atrioventricular conduction, increased cardiac index, coronary blood flow and stroke work and a decrease in peripheral resistance and arteriovenous oxygen difference. Mean arterial blood pressure and stroke volume remain unchanged or decrease.[9–15]

In addition to the favorable hemodynamic effects of isoproterenol, its striking effectiveness on the sinoatrial and ventricular pacemakers and its minimal action on myocardial automaticity[15,16–19] suggest that this drug may be of value in acute myocardial infarction when an increase in myocardial automaticity is undesirable. Of interest are the reports of ventricular tachycardia and fibrillation successfully treated with isoproterenol.[20–22] For these reasons, Robbin et al.[22] believe isoproterenol to be the safest drug for use in Morgagni-Adams-Stokes syndrome when alternating ventricular tachycardia and ventricular asystole occur in the same patient.

Others using isoproterenol have noted excessive tachycardia with restoration of sinus rhythm, atrial fibrillation-flutter, ventricular flutter-fibrillation and marked ventricular slowing with asystole.[23–25] Chandler and Clapper

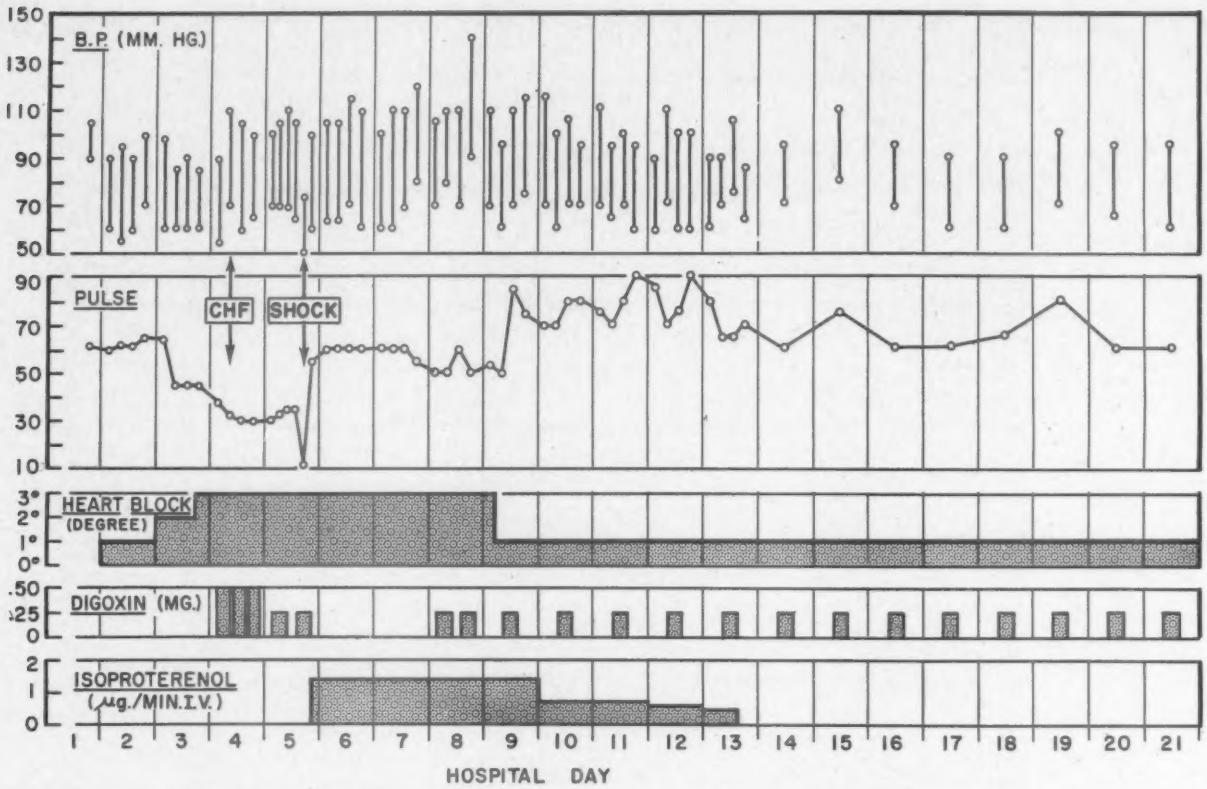


FIG. 5. Graphic summary of patient's hospital course. B.P. = blood pressure; CHF = congestive heart failure.

have reported slow ventricular tachycardia following a large overdose of isoproterenol parenterally.[24] The reported safety of isoproterenol may be dependent on whether the desired chronotropic response is obtained with small doses of the drug.

Gale and Enfroy[26] have reported a case of acute myocardial infarction complicated on the fourth day by complete heart block with Morgagni-Adams-Stokes attacks successfully treated with continuous parenteral administration of isoproterenol. No mention was made of the exact rate of administration or of any immediate changes in the pacemaker except that the rate was increased sufficiently to prevent further attacks. The complete heart block spontaneously disappeared on the second day.

In the present case the low requirement of 1.4 μg. per minute of isoproterenol may have accounted for the lack of prefibrillation activity. Although no side effects occurred following the administration of isoproterenol, sweating, palpitations, angina and pulmonary edema have been reported.[23] The improvement in atrioventricular conduction, the increase in atrial and ventricular rate, and elevation of the pacemaker to higher centers are well illustrated in our case and suggested the block would be transient.[23] The ease with which isoproterenol restored the pacemaker suggested an improved prognosis. Rarely have patients with persistent complete heart block complicating acute myocardial infarction survived.[1] Elevation of the pacemaker by isoproterenol to the sinoatrial node in cases of Morgagni-Adams-Stokes attacks secondary to transient complete heart block has been noted by Schwartz and Schwartz.[23] Schumacher and Schmock[20] have noted consistent elevation of the pacemaker to the level of the atrioventricular node.

Digitalis is a not infrequent cause of complete heart block and it is possible that its use aggravated the recently developed heart block in this patient. For this reason it was omitted for two days even though it had improved the acute heart failure. If digitalis did play some part in the acute ventricular bradycardia, it is of great interest that its effects were reversed by isoproterenol. Certainly, the use of isoproterenol in complete heart block secondary to digitalis deserves further study.

As the acute heart block complicating myocardial infarction is usually transient, the judicious use of isoproterenol may be hoped to

result in a reduced mortality rate. The sublingual form of isoproterenol may be used initially. If the response is poor or Morgagni-Adams-Stokes attacks persist the parenteral form, which has been successful in patients where the sublingual form has failed, should be administered.[24,27] A trial of 0.02 mg. intravenously over a sixty second period with constant electrocardiographic monitoring may indicate whether continuous isoproterenol will be effective. If a satisfactory response is obtained, continuous parenteral isoproterenol with its rapid onset of action and short duration of action will provide a means of precise regulation at the desired rate.

Summary

A case of acute myocardial infarction complicated by complete heart block successfully treated with continuous intravenous administration of isoproterenol is reported. This complication should be anticipated in all cases of acute myocardial infarction especially with inferior wall involvement. It is hoped that the increasing use of isoproterenol, as well as steroids and electrical pacemakers, will result in an overall lowering of the mortality rate in this condition.

Addendum

Since the completion of this case report two additional patients with inferior wall myocardial infarction complicated by acute complete heart block have been successfully treated with continuous parenteral isoproterenol at a rate of 1 to 3 μg. per minute for similar periods of time.

References

1. Penton, G. B., Miller, H. and Levine, S. A. Some clinical features of complete heart block. *Circulation*, 13: 801, 1956.
2. Crow, J. C. and White, P. D. Complete heart block: a follow-up study. *Ann. Int. Med.*, 49: 260, 1958.
3. Wright, J. C., Hejtmancik, M. R., Herrmann, G. R. and Shields, A. H. A clinical study of complete heart block. *Am. Heart J.*, 52: 369, 1956.
4. Imperial, E. S., Carfallo, R. and Zimmerman, H. A. Disturbances of rate, rhythm and conduction in acute myocardial infarction. A statistical study of 153 cases. *Am. J. Cardiol.*, 5: 24, 1960.
5. Rosenbaum, F. F. and Levine, S. A. Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. *Arch. Int. Med.*, 68: 913, 1941.
6. Cohen, D. B., Doctor, L. and Pick, A. The significance of atrioventricular block complicating acute myocardial infarction. *Am. Heart J.*, 55: 215, 1958.
7. Starzl, T. E., Gaertner, R. A. and Baker, R. R. Acute complete heart block in dogs. *Circulation*, 12: 82, 1955.
8. Starzl, T. E. and Gaertner, R. A. Chronic heart block in dogs: a method for producing experimental heart failure. *Circulation*, 12: 259, 1955.
9. Stack, M. F., Rader, B., Sobol, B. J., Farber, S. J. and Eichna, L. W. Cardiovascular hemodynamic functions in complete heart block and the effect of isopropylnorepinephrine. *Circulation*, 17: 526, 1958.
10. McGaff, C. F., Cohen, N. K. and Leight, L. Hemodynamic effects of isoproterenol in complete heart block. *Arch. Int. Med.*, 104: 242, 1959.
11. Barcroft, H. and Konzett, H. On the actions of noradrenaline, adrenaline and isopropyl noradrenaline on the arterial blood pressure, heart rate, and muscle blood flow in man. *J. Physiol.*, 110: 194, 1949.
12. Melville, K. I. and Lu, F. C. Effects of ephedrine, phenylephrine, isopropylarterenol and methoxamine on coronary flow and heart activity as recorded concurrently. *Arch. Int. Pharmacodyn.*, 92: 108, 1952.
13. Darby, T. D., Watton, R. P. and Gazes, P. C. Effects of drugs on ballistocardiographic recordings. *Am. J. Cardiol.*, 3: 668, 1959.
14. Lands, A. M. and Howard, J. W. A comparative study of the effects of l-arterenol, epinephrine and isopropylarterenol on the heart. *J. Pharm. & Exper. Therap.* 106: 65, 1952.
15. Boyer, S. H. and Chisholm, A.W. Chronotropic responses to sympathomimetic amines in experimental complete heart block: the influence of pentobarbital, hydrocortisone, and acid-base changes. *Bull. Johns Hopkins Hosp.*, 103: 47, 1958.
16. Roberts, J., Standgert, F., Kim, Y. I. and Riker, W. F., Jr. The initiation and pharmacological reactivity of a ventricular pacemaker in the intact animal. *J. Pharm. & Exper. Therap.*, 117: 374, 1956.
17. Garb, S. and Chenoweth, N. J. Studies on hydrocarbon-epinephrine induced ventricular fibrillation. *J. Pharm. & Exper. Therap.*, 94: 12, 1948.
18. Nathanson, M. H. and Miller, H. The action of norepinephrine, epinephrine and isopropyl norepinephrine on the rhythmic function of the heart. *Circulation*, 6: 238, 1952.
19. Nathanson, M. H. and Miller, H. Effect of 1-(3,4, dihydroxyphenyl)-2-isopropylaminoethanol (isopropylnorepinephrine) on the rhythmic properties of the human heart. *Soc. Exper. Biol. & Med.*, 70: 633, 1949.
20. Schumacher, E. E. and Schmock, C. L. The control of certain cardiac arrhythmias with isopropylnorepinephrine. *Am. Heart J.*, 48: 933, 1954.
21. Kayden, H. J. and Stack, M. Studies on complete atrio-ventricular dissociation with special reference to Stokes-Adams syndrome. *Circulation*, 12: 729, 1955.

22. Robbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S. Adams-Stokes syndrome. The treatment of ventricular asystole, ventricular tachycardia and ventricular fibrillation associated with complete heart block. *Am. J. Med.*, 18: 577, 1955.
23. Schwartz, S. P. and Schwartz, L. S. The Adams-Stokes syndrome during normal sinus rhythm and transient heart block. I. The effects of isuprel on patients with the Adams-Stokes syndrome during normal sinus rhythm and transient heart block. *Am. Heart J.*, 57: 849, 1959.
24. Chandler, D. and Clapper, M. I. Complete atrioventricular block treated with isoproterenol hydrochloride. *Am. J. Cardiol.*, 3: 336, 1959.
25. Friedberg, C. K., Kahn, M., Scheuer, J., Bleifer, S. and Dack, S. Adams-Stokes syndrome associated with chronic heart block. Treatment with corticosteroids. *J.A.M.A.*, 172: 1146, 1960.
26. Gale, H. H. and Enfroy, H. L. Stokes-Adams attacks complicating acute myocardial infarction: their treatment with continuous intravenous infusion of isopropylnorepinephrine. *New England J. Med.*, 260: 1229, 1959.
27. Robbin, S. R. and Dack, S. Treatment of Stokes-Adams attacks in heart block with special reference to parenteral, sublingual and long acting isoproterenol. *Circulation*, 20: 757, 1959.

Atrial Flutter with 1:1 A-V Conduction*

GEORGE A. RUBEIZ, M.D. *and* SAMI KAID BEY,† M.D.

Beirut, Lebanon

THE RATE OF atrial flutter contractions is usually 220 to 400 per minute with varying A-V conduction ranging between 2:1 and 4:1 and in some cases 6:1 to 8:1. On rare occasions the refractory period of the A-V node decreases suddenly and all atrial stimuli are transmitted, resulting in the condition of atrial flutter with 1:1 A-V conduction.

The ventricular rate in atrial flutter with 1:1 A-V conduction is usually 220 to 300 per minute.[1] This is associated frequently with a fall in cardiac output and signs and symptoms of peripheral circulatory failure or pulmonary congestion. Bourne[2] reported the death of a patient in whom the condition persisted for seven days.

This paper reports a patient with long-standing atrial flutter treated with digitalis and quinidine who had repeated episodes of 1:1 A-V conduction following physical exertion.

CASE REPORT

A thirty-six year old Palestinian man was first admitted to the American University Hospital in May 1948 because of sudden brief attacks of palpitation of six months' duration, usually precipitated by exertion and heavy meals. The electrocardiogram on admission revealed atrial flutter with 2:1 to 3:1 A-V conduction and an average ventricular rate of 140 per minute. Quinidine sulfate, 0.2 gm., was given every three hours; after 3.4 gm. had been administered reversion to normal sinus rhythm occurred. Although regular maintenance therapy with quinidine was not adhered to, the patient did not have another attack until 1954 when he experienced an attack of palpitation. Quinidine was administered and the arrhythmia subsided shortly thereafter. He was free of symptoms until July 1956 when he suffered another mild attack of palpitation similar to that of 1948. The electrocardiogram taken by his private physician showed atrial flutter. Quinidine followed by digitalis and various sedatives failed to stop the arrhythmia and he was admitted to the American University Hospital for the second time on November 12, 1956.

Course During Second Admission: The blood pressure was 125/85 mm. Hg, the pulse 104 per minute and regular. There was no detectable enlargement of the heart. A soft apical presystolic murmur was suspected. The hemogram, urine analysis, blood urea nitrogen and fasting blood sugar were within normal limits. The electrocardiogram showed atrial flutter with 2:1 and 3:1 A-V conduction. The atrial rate was 300 per minute and the ventricular rate 130 per minute. Cardiac x-ray series showed moderate enlargement of the left atrium. Clinical diagnosis was rheumatic heart disease with mild mitral stenosis.

The patient was redigitalized with 3 mg. of digoxin during the first two days and then was maintained with 0.25 mg. a day. Quinidine sulfate, 2 gm., was administered every day. There was no effect on the arrhythmia. Quinidine was discontinued and the patient left the hospital. Following discharge the attacks of palpitation persisted. He was taking the digoxin regularly until April 1958 when he stopped all medications. He was readmitted to the American University Hospital on January 9, 1959 for the same complaint.

Course During Third Admission: The blood pressure was 130/90 mm. Hg; pulse, 100 per minute; cardiac findings were unchanged. The electrocardiogram on admission (Fig. 1) revealed atrial flutter with 4:1 and 3:1 A-V conduction, with an atrial rate of 300 per minute. Digitoxin, 2.2 mg., was given in the first five days and 0.2 to 0.3 mg. daily thereafter. The ventricular rate fell to 90 per minute but the flutter persisted. Quinidine was added. The first day the patient received 0.4 gm. of quinidine sulfate orally every two hours for five doses. The second and third days he received a total dose of 3 gm. The flutter rate dropped from 300 per minute on admission to 250 after administration of quinidine (Fig. 2A). After the second day of quinidine therapy attempts to leave the bed were associated with palpitation and syncope. Atrial flutter with 1:1 A-V conduction was suspected.

Figure 2B shows the effect of getting out of bed on the A-V conduction and the ventricular rate. The 2:1 A-V condition changed to 1:1 with increase of ventricular rate from 100-125 to 250. This was associated with fall in blood pressure and

* From the Department of Internal Medicine, American University Hospital, Beirut, Lebanon

† Present address: New England Deaconess Hospital, Boston, Massachusetts.

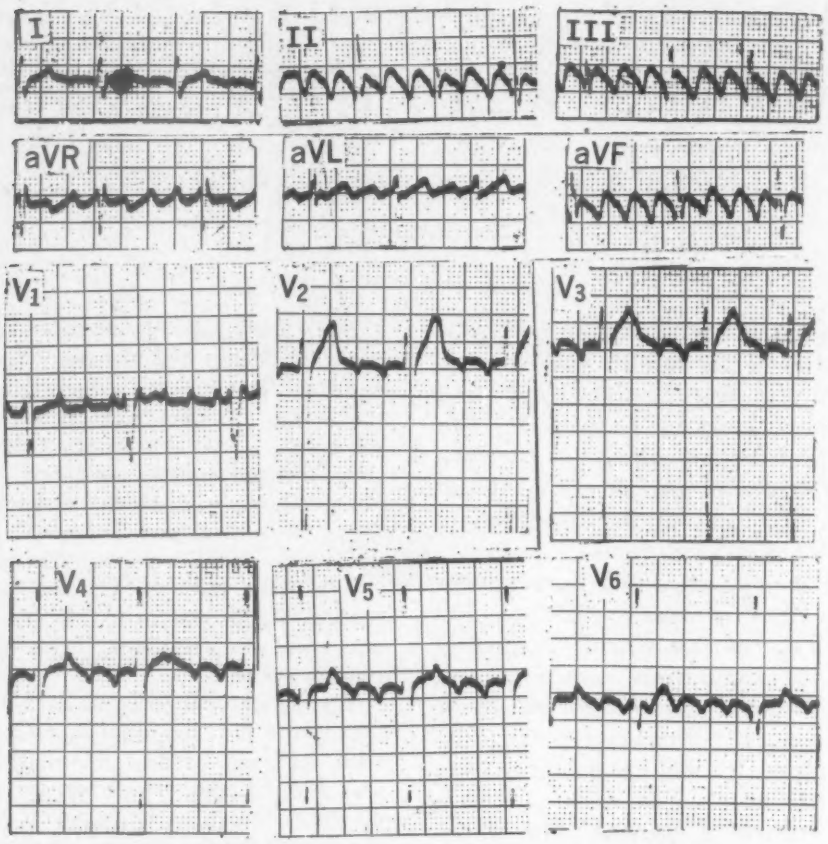


FIG. 1. January 13, 1959. Twelve lead electrocardiogram obtained before quinidine therapy. The atrial flutter rate is 300 per minute with a varying A-V conduction (3:1, 4:1).

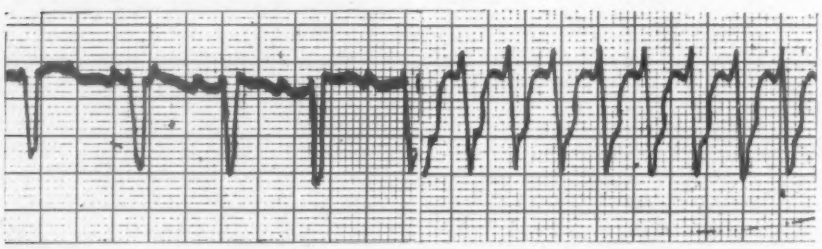


FIG. 2. A, control. Lead V_1, taken at rest after quinidine therapy. The atrial flutter rate has decreased to 250 per minute. B, exercise. Lead V_1, taken immediately after patient got out of bed. It reveals atrial flutter with 1:1 conduction. Note that the ventricular rate is exactly 250 per minute.

syncope. Figure 3 records the same changes occurring when the experiment was repeated on another occasion. It was decided to discontinue the administration of quinidine and to continue maintenance doses of digitoxin. Figure 4 shows the same experiment as above two weeks after discontinuing quinidine. This time exercise was not followed by 1:1 atrioventricular conduction.

COMMENTS

Atrial flutter with 1:1 A-V conduction is a rare condition; fifty-one cases are reported in the literature.[3–6] The development of 1:1 A-V conduction usually follows quinidine therapy, exercise or emotional disturbance.[3] Scott[7] reported a case of atrial flutter in which 1:1 A-V conduction followed exercise. Quinidine therapy is responsible for many cases; so much so that it has become common practice to administer digitalis prior to quinidine therapy.[8] On the other hand, digitalis does not always prevent the development of 1:1 A-V conduction. Failure of digitalis to prevent this is

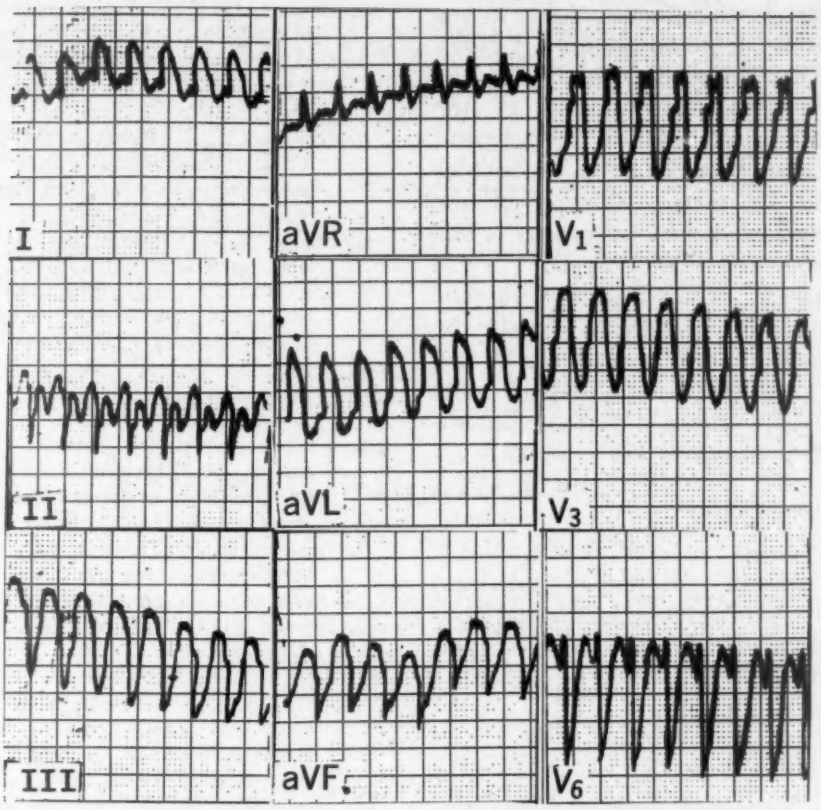


FIG. 3. Electrocardiogram taken about half an hour after the one shown in Figure 2, also after exercise. There is atrial flutter with 1:1 A-V conduction at a ventricular rate of 250 per minute. QRS duration 0.12 second. Note resemblance to ventricular tachycardia.

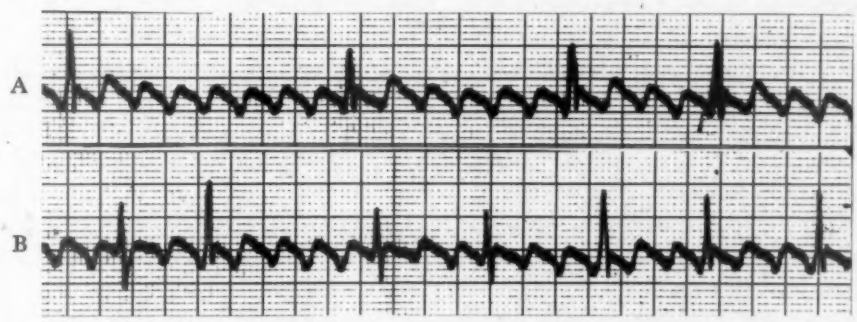


FIG. 4. A, control (lead II). Atrial flutter (atrial flutter rate 300 per minute) with varying A-V conduction, 4:1 — 8:1. B, lead II. Taken after exercise. Atrial flutter (atrial flutter rate, 330 per minute) with varying A-V conduction, 2:1 — 5:1, mainly 3:1 conduction.

shown by the present case. Similarly, London and Howell[9] previously reported a patient with atrial flutter who had 1:1 A-V conduction on three occasions during administration of quinidine despite the concomitant use of digitalis.

Quinidine is known to decrease the flutter rate, thereby facilitating atrioventricular conduction.[4,10,11] In our case the atrial flutter rate decreased from 300 to 250 per minute, with quinidine. Exercise in the presence of a slower atrial rate further decreased A-V block, resulting in atrial flutter with 1:1 A-V conduction. Although digitalis increases A-V block, exercise in digitalized patients with persistent flutter may temporarily decrease the grade of block and thus produce periods of rapid ventricular rate.[12] It is believed that sedation and rest are advisable whenever quinidine is used to revert atrial flutter. The

electrocardiograms in this case conform to the criteria of Finkelstein, Gold and Bellet.[3] "Functional fatigue of the branches secondary to the rapid rate"[3] increases the duration of the QRS. In Figure 3 the QRS is 0.12 second in duration and the resemblance to ventricular tachycardia may be seen. Slowing of the ventricular rate was followed by return of the QRS duration to normal limits (Fig. 4).

The treatment of atrial flutter with 1:1 A-V conduction should be energetic because the prognosis depends on the duration of the attack. Vagal stimulation is of help in some cases. If this fails, large doses of digitalis (preferably intravenously) should be used.[3]

Summary

Atrial flutter with 1:1 A-V conduction developed in a patient receiving digitalis and quinidine. The role of exercise in this development is demonstrated. It is concluded that sedation and rest should accompany the therapy of atrial flutter with quinidine.

References

1. Arenberg, H. Paroxysmal auricular flutter with 1 : 1 auriculo-ventricular ratio. *Ann. Int. Med.*, 8: 951, 1935.
2. Bourne, G. Paroxysmal auricular flutter. *Lancet*, 1: 686, 1933.
3. Finkelstein, D., Gold H. and Bellet, S. Atrial flutter with 1 : 1 A-V conduction. *Am. J. Med.*, 20: 65, 1956.
4. Spivack, A. P., Sackner, M. A. and Schnabel, T. G. Atrial flutter with 1 : 1 A-V conduction associated with pulmonary embolism in the aged. *Am. Heart J.*, 59: 53, 1960.
5. Marks, J. Atrial flutter with 1 : 1 A-V conduction. *Arch. Int. Med.*, 100: 989, 1957.
6. Willis, W. H. and Steele, K. C. Atrial flutter with 1 : 1 A-V conduction corrected by mitral commissurotomy. *Am. Heart J.*, 54: 638, 1957.
7. Scott, R. W. A case of auricular flutter with paroxysmal attack of 1 : 1 conduction. *J. A. M. A.*, 79: 1984, 1922.
8. Tendowsky, R. M., Oyster, J. M. and Silverglade, A. The combined use of lanatoside C and quinidine in the abolition of auricular flutter. *Am. Heart J.*, 32: 617, 1946.
9. London, F. and Howell, M. Atrial flutter; 1 : 1 conduction during treatment with quinidine and digitalis. *Am. Heart J.*, 48: 152, 1954.
10. Levine, S. A. Clinical Heart Disease, 5th ed., p. 493. Philadelphia, 1958. W. B. Saunders & Co.
11. Blinder, H., Burstein, J., Horowitz, W. and Gersh, E. Intravenous quinidine therapy for auricular flutter resulting in 1 : 1 auricular flutter and other changes. *New York State J. Med.*, 50: 298, 1950.
12. Herrmann, G. and Hejtmancik, M. R. Atrial flutter: methods of treatment. *Am. Heart J.*, 41: 182, 1951.

Workmen's Compensation for the Cardiac

Edited by Louis H. Sigler,† M.D., F.A.C.C.

Brooklyn, New York

Emotional Disturbance and Myocardial Infarction*

The object of this column is to attempt to establish criteria on causal relationship between physical or emotional strain and cardiac disability in workmen's compensation. We invite free and open discussion of factual value from all readers.

In the September 1960 issue of the Journal we published a case report submitted by Dr. Romeo J. LaJoie of Los Angeles which was considered to illustrate causal relationship between a severe emotional disturbance induced by witnessing a midair explosion of an airplane and an attack of myocardial infarction. I am glad that the case has stimulated the following discussions from three readers of the Journal.

Letter to Editor

Dear Editor:

I have received every issue of the American Journal of Cardiology and have, in general, considered it excellent. The section that chronically distresses me is Workmen's Compensation for the Cardiac by Dr. Louis H. Sigler. We are faced with an aging population and I, for one, would like to keep the oldsters working. I have been very impressed with the therapeutic value emotionally and physically to the cardiac patient of returning to useful activity. It benefits patients to perform to their fullest capacity and I like to see employers permit them to do so. This seems to be as important as any drug, and more important than most.

The way Dr. Sigler interprets causation fails to meet sound scientific criteria. More important than this is that if his criteria are generally accepted, it will soon be impossible for any employer to provide work for any but those in perfect physical condition. The September 1960 issue (Vol. vi, p. 697) contains his comments under "Acute Myocardial Infarction Following an Emotional Disturbance." If I interpret his comments correctly, he would hold the airline company responsible and liable under these circumstances. This distresses me greatly for I believe he tends to help this individual financially now at the risk of jeopardizing employability of the multitude for the future. Is this a true cause of myocardial infarction or is it simply an incident bringing his true disease to light? Is this fair to the insurance companies, compensation funds, etc? Is it fair to the individual himself to put his future employability at stake and to rob him of his own responsibility? Is this fair to all cardiac patients who most likely will have far more difficulty in finding employment with frightened employers due to stretching of incidental factors into a causative position?

Am I completely out of step in my reasoning? I would appreciate very much a sounding out of responsible cardiologists across the country, if this can be arranged.

Clarence E. Hicks, M.D.
Hereford Medical and Surgical Clinic
Hereford, Texas

* The opinions expressed in this paper are those of the author and do not necessarily reflect the opinion of the American College of Cardiology or the Workmen's Compensation Committee.

† Chairman, Workmen's Compensation Committee, American College of Cardiology.

Reply by Dr. Sigler

The object of the section on workmen's compensation in the Journal is to stimulate thought and research in this important and neglected field. My first two papers on the subject have been published elsewhere, not in The American Journal of Cardiology.[1,2] The subject matter of both of those papers has been widely accepted with universally favorable comment.

I appreciate the fact that we know little of the etiology and pathogenesis of coronary atherosclerosis and of the factors that bring about an acute insult. Because of the inadequacy of such knowledge we have no authorities in this field. Opinions are based purely on assumptions and theoretic considerations, most of which are not in conformity with reality. For instance, the theory that atherosclerosis is an aging process or is due to hypercholesterolemia disregards the pathologic-physiologic changes that may be induced in the course of time by altered hemodynamics which vary with different persons and which may be the main underlying causes. It also disregards a great many other deleterious conditions which may affect the vascular system during life, emotional and physical strain being some of them. It is true that during the course of coronary disease an emotional or physical strain may be an "incident bringing his true disease to light" as Dr. Hicks states in the case he refers to, but the incident is a reality. There is no question that there was pre-existing coronary disease in this case but I should like to have some "authority" *prove* that the severe emotion could not bring about the sudden acute coronary changes. I should also like to have someone *prove* that the cumulative effect of emotional or physical strain over years had absolutely nothing to do with the development of the degenerative changes.

Dr. Hick's fear that the compensation factor may affect the employability of subjects in the older age groups is perfectly well founded. This is a problem, however, for the legal profession and for industry to solve, not for the physician. Some changes in the compensation laws which would recognize that only part of an acute cardiac insult caused by strain is due to such strain and the responsibility be borne jointly by the employer and by some health agencies, may be one of the necessary changes. The essential part the physician can play is to help rehabilitate the patient and return him to work as quickly as possible. In my experience upward of 80 per cent of patients in private practice return either to their original work or to some modified routine following recovery from myocardial infarction. Once we can demonstrate to industry that coronary disease is compatible with normal or nearly normal activity the fear of employing such persons will be greatly allayed. Another part a physician can play is to help eliminate unwarranted and outright fraudulent claims.

It must be recognized that the number of cardiac disability claims due to strain or trauma is comparatively small in proportion to the working population and the relatively few cases should not be cause for alarm or for maladministration of justice.

Follow-up Study of the Reported Case

The aforementioned case did become a workmen's compensation claim. Dr. Irving I. Lasky of Beverly Hills, California, who originally did not agree with the theory that the attack of myocardial infarction was due to emotional upset later reviewed the Industrial Accident Commission files in this case and quoted the following statement from the records. "The patient did not have symptoms during the explosion of the aircraft. While proceeding at a fast pace to the operations office on the field, he was stricken by a severe pain in the chest." He therefore concluded that "although there is no question but that the patient undoubtedly suffered great anxiety with reference to witnessing the midair explosion, an added factor in this pathogenesis is the physical effort involved in walking at a fast pace to the operations office. I do not feel that there is justification for ascribing the incident entirely to emotional disturbance."

We must agree that with our present knowledge the serious effect on the heart of a severe emotional disturbance leaves some doubt in our minds as to causal relationship, and we have a tendency to look for some physical factor to explain an attack even though the physical factor was only "walking at a fast pace," which in itself was not of severe enough nature to cause a myocardial infarction. In association with the severe emotional strain, however, some physical strain might be an added factor.

In a previous report[3] I have shown causal relationship between an acute attack of myocardial infarction and extreme emotional upset

and have also quoted Spencer[4] who presented a case with recurring myocardial ischemia and final death after repeated nervous disturbances.

In this respect the following interesting case also definitely appears to prove that a severe emotional upset alone is enough to bring about an attack. The case has great value because it had no compensation angle and the facts therefore cannot possibly be biased.

References

1. Sigler, L. H. Cardiac disability and death caused by strain. *J. A. M. A.*, 154: 294, 1954.
2. Sigler, L. H. The evaluation of claims for workmen's compensation in cardiac disability and death. *J. Indust. Med. & Surg.*, 25: 10, 1956.
3. Sigler, L. H. Emotional disturbances as a cause of an acute cardiac insult. *Am. J. Cardiol.*, 4: 557, 1959.
4. Spencer, R. Speculations concerning the influence of psychoneurosis on cardiac pain. *U.S. Armed Forces M. J.*, 9: 1184, 1958.

Acute Myocardial Infarction Precipitated by Severe Emotional Disturbance*

Morton Morris Pinckney, M.D.

Richmond, Virginia

A fifty-three year old moderately hypertensive white woman who worked as a clerk in a local hospital was told that her son had been brought into the emergency room dead as a result of accidental electrocution. The mother began to cry and scream and soon complained of "pain in the heart." She was carried to the emergency room, alternately sobbing or screaming hysterically, and complaining of pain just to the left of the sternum. Her blood pressure at first was 182/124 mm. Hg and soon fell to 160/100. The heart rate was rapid and a protodiastolic gallop rhythm was present. An electrocardiogram (Fig. 1B) showed a rate of 100 and some elevation of the S-T takeoff in lead I, flattening of T in aVL and small R waves in leads V_1, V_2 and V_3. She was admitted to the hospital with a tentative diagnosis of myocardial infarction. Her blood pressure varied between 140/90 and 170/100 and her pulse between 90 and 100 per minute. About four hours after admission the attending nurse reported that the systolic blood pressure had fallen to 90 and that the nail beds were cyanotic. Oxygen by nasal catheter was given immediately. Examination revealed rales in the bases of the lungs.

A second electrocardiogram (Fig. 1C) approximately five hours after the first tracing showed a small Q wave, an elevated S-T takeoff and inverted T in leads I and aVL, isoelectric T waves in V_5 and V_6 and inverted T waves in V_3 and V_4, consistent with anterolateral wall infarction.

A third electrocardiogram on the following day (Fig. 1D) showed a small Q, elevated S-T takeoff and inverted T in lead I and inverted T waves in lead II, aVL and V_2 to V_6, and coving of the S-T segment in V_3 and V_4. On this day the serum glutamic oxalacetic (SGO-T) transaminase was 42 units, and the leukocyte count was 15,000 with 79 per cent polymorphonuclear leukocytes. The next day the SGO-T fell to 26.

On the third day after admission the electrocardiogram (Fig. 1E) showed a prominent Q in lead III with a slightly elevated S-T segment; also a depressed S-T takeoff and a sharply inverted T wave in V_2 through V_6. The negativity of the T waves diminished four days later (Fig. 1F). Two months later the electrocardiogram (Fig. 1G) showed marked improvement and began to assume the appearance of the record obtained about nine months before the attack (Fig. 1A).

The patient's subsequent course was characterized by marked mental depression and considerable pains of a more or less vague nature. She showed a good response to lanatoside C (Cedilanid®) and thereafter maintained good

* From the Richmond Memorial Hospital, Richmond, Virginia.

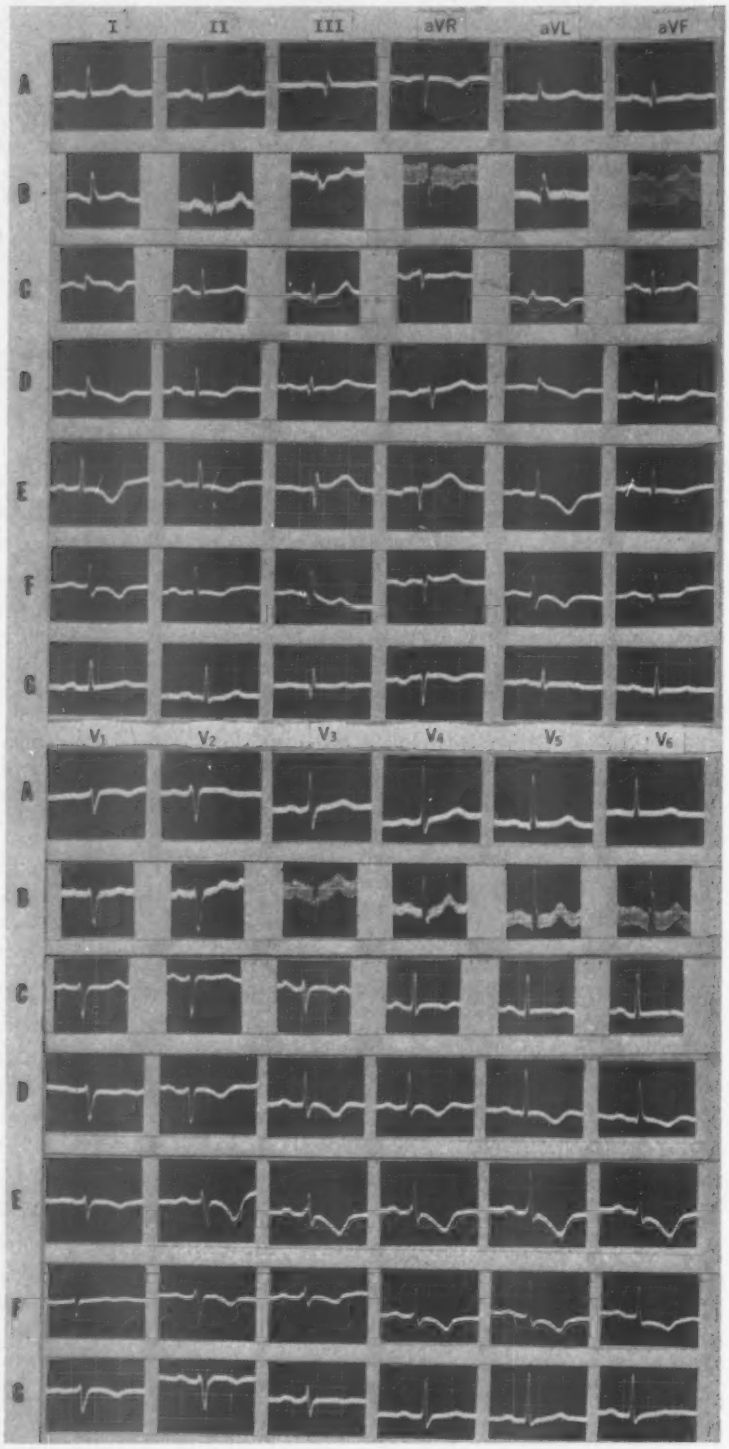


FIG. 1. A, about nine months before attack; tracing normal. B, soon after onset of attack. C, about five hours after B; features of anterolateral wall infarction. D, the following day. E, two days after D; extensive subendocardial myocardial ischemia and necrosis of anterior wall. F, four days after E; improvement in the ischemic pattern. G, two months after F; some residual damage as compared with A.

compensation on digitalis. Her blood pressure readings varied from 140/80 to 125/82 mm. Hg.

Her son's death occurred on August 17, 1959, and the patient still complains of weakness and disability in December 1960.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Readings in Cardiology

From time to time, interesting books which ordinarily might escape the attention of cardiologists will be briefly reviewed in these columns.

Cardiac Pain: We, as cardiologists, tend to consider angina pectoris and acute myocardial infarction as merely aspects of the same disease, coronary artery disease. Two recent books should help make us aware that the relationship between these two conditions is not necessarily so simple. In Dr. Beecher's book,* the chapter, Pathology and Pain, should be read by all. He points out that the sensation pain or suffering is made up of two components: (1) the original sensation, and (2) the psychic modification of this sensation. He illustrates this by describing his experiences on the Anzio Beachhead during World War II. He explains the reason for the lack of pain of many wounded soldiers as a sign that the wounds these men received comprised a ticket to the safety of the hospital. The war was over for them. Conversely, about 50 per cent of civilians undergoing surgery had enough postoperative pain to want something done about it. To civilians, the necessity for surgery was a disaster and the surgical wound a symbol of this. In short, the significance of the wound apparently determines the suffering from it. He further points out that anxiety constitutes one of the basic elements in the pain process. This is a concept to remember whenever we treat a patient with pain due to angina pectoris or myocardial infarction.

Dunbar† has described changing concepts of disease and has pointed out the importance of psychologic and environmental factors in various psychosomatic diseases. She writes that the history of patients with coronary thrombosis reveals "a relatively high family history of cardiovascular disease with an even higher exposure to cardiovascular disease or to sudden death with little accident history but rather frequent mention of nervousness. There is likely to have been close contact with parents and a somewhat rigid family pattern which usually tends to persist through life.

"Patients' previous health records are often poor, largely as a result of a tendency toward self-neglect, but rarely incapacitating. They report few accidents or injuries. The accidents reported are mostly the result of attacks provoked by the patient. These patients may get a broken nose as a reward for a sharp remark, but they do not have slipping, falling, or traffic accidents.

"Their pattern of adjustment is marked by a tendency to complete educational units undertaken, work to the top, and their income and vocational level is relatively high. They are essentially extroversive, generally respected and in spite of a tendency to dominate, establish good interpersonal relationships with men through argument and women through attention. They adhere to the role of exemplary husband and father, and when frustrated take recourse in sexual promiscuity about which they become anxious and worried.

"As children they were inclined to be hostile toward their fathers, docile, although often hostile and fearful toward their mothers. They step naturally into the role of head of the house and 'carry the burden' in return for which they expect care and consideration. Physical and emotional pain is disregarded because nothing can interfere with their drive to work; and weakness or depression which they occasionally feel cannot be admitted. They take stimulants not so much for fun as to spur them on. In

* Disease and the Advancement of Basic Science. Edited by Beecher, H. K., M.D. Cambridge, 1960. Harvard University Press.

† DUNBAR, F. Psychiatry in the Medical Specialties. New York, 1959. Blakiston Division, McGraw-Hill.

their interests they conform with the group in which they wish to succeed—theatre, books, music, sports, as the fashion dictates. They have a strong sense of right and wrong but are skeptical about religion. They must keep busy but always working toward a goal. In contrast it is the need to avoid that impels the accident-prone to keep busy doing this or that, so vigorously and incessantly that one of them was nicknamed the 'thing-doer.'

"The trigger situation which precipitates the coronary accident is exposure to shock, particularly one which takes the form of ego-insult. Unlike the accident patient, they have a marked identification with authority and authoritarian concepts" (page 87).

"The history of a patient with the anginal syndrome or an atypical coronary differs from that just outlined for coronary patients in the following ways:

"1. In spite of their tendency to minimize symptoms and neglect their bodies, they have had more major illnesses and major operations then the typical coronary patient. This diversity of somatization may have the effect of diverting some anxiety away from the cardiovascular system.

"2. Having the coronary patient's tendency to work to the top in their diverse fields and reach a high income level, they are likely to choose an occupation in which competition is only moderately close and intense, for example, a small business or an artistic career where individual differences rather than conformity are respected.

"3. They allow themselves more enjoyment along with their work and have more of a fantasy life than the typical coronary patient.

"4. But, at the same time, they are far more conscious of anxiety and fear and in consequence neurotic traits are more obvious, usually in the form of phobias and nightmares.

"5. As a rule they remain satisfied in imitating father rather than in attempting to out-do and subdue him.

"It has been suggested that in young people presenting the anginal picture, the prognosis relative to the development of coronary damage depends considerably on vago-sympathetic equilibrium. This varies with the degree of crystallization of a rigid life pattern and the extent of emotional outlets. In any case, these patients seem to be able to live many years without a vascular accident. While predominantly extratensive like the coronary disease group, they are less restricted and show a greater degree of spontaneity and a higher coefficient of homeostatic elasticity. They are more willing to let down their barriers and establish contact with the physician" (page 97).

College News

PRESIDENT'S COLUMN

The College and The American Heart Association

MANY OF YOU have naturally been interested in our relations with the AHA; you have known that for two years we have had a continuing liaison committee and have been holding concurrent meetings with the AHA. There were at one time rumors of difficulties between the two organizations and I wish to assure you that these rumors are, on an official basis, completely unfounded. The relationship between the College and the AHA is one of mutual helpfulness and this has actually been achieved by continued personal contact between the officers and the office staffs of the two groups.

No one can seriously challenge the preeminence of the AHA in the total picture of American cardiology, in the fields of public information, support of research and professional education, community service and public health. Indeed every one of our members must emphasize his interest in cardiology by actual support of the Association's program and by membership in American Heart Association.

In its turn, the AHA has full cognizance of the value of our College work in the field in which the College operates. The College is interested in the accredited specialist and in those who seek to carve out for themselves careers as accredited specialists in cardiology. We do not duplicate any part of the heart program except in this one field, but here we are dedicated to a standard of progress and excellence that must be judged on the factual basis of our achievement.

We are willing to abide by that judgment. This month we are having our Tenth Annual Convention and a sober study of the content of this convention program will give an accurate picture of the level of our College work. Also, this month we are publishing our Directory and here again, a study of the names of those who are associated in our work will give a picture of the College as people. The Journal in which these very notes are published is further evidence of College achievement; our Encyclopedia is a towering monument to our serious purpose.

For the past two years we have experimented with methods of achieving a working basis of cooperation between the College and the Association. In lieu of our Eighth and Ninth Interim Meetings, the College put on its Fireside Conference series as a part of the Thirty-second and Thirty-third Annual Meetings of the AHA. At our Eighth Annual Meeting the Association had a special exhibit to commemorate its tenth anniversary of work with the National Heart Institute; at our Ninth Annual Meeting, one entire scientific session was presented by the Association. It was our hope that these concurrent efforts would point the way to a permanent pattern.

Most of us felt that the joint effort programs were an enrichment for both organizations, and we of the College wanted to continue along these lines. However, since the liaison committee was not able to reach an agreement on permanent affiliation, the Association discontinued the arrangement for joint meetings. This year we will have no joint meeting in October. Since it is too late for us to set up our usual interim meeting, I personally urge all of you to attend the Thirty-fourth Annual Meeting of the American Heart Association in Miami.

The question of affiliation, therefore, still remains an open one, and we are still searching for a satisfactory pattern. Your officers and trustees are committed to our constitutional necessity for preserving the identity and sovereignty of the College. Whatever affiliation is effected it must be within the legal necessities of our corporate framework.

It has been our feeling that the goals that we have won through our first decade must remain, and the leadership that has attained these goals must not lightly be changed. We have proved our dedication to an ideal of excellence in our specialty. Any affiliation which we work out must guarantee that that standard will be secure.

LOUIS F. BISHOP, M.D., *President*

AMERICAN COLLEGE OF CARDIOLOGY

Tenth Annual Meeting

May 17–20, 1961, Biltmore Hotel, New York, New York

Scientific Program

Investigators Session

Wednesday, May 17, 9:00 a.m.–12:00 p.m.

SYMPOSIUM ON

METHODS OF MEASUREMENT OF OXYGEN IN BLOOD

Co-Chairmen: RICHARD GORLIN, M.D.
JOHN L. PATTERSON, M.D.

1. Introductory Remarks.
   RICHARD GORLIN, M.D., and JOHN L. PATTERSON, M.D.
2. Spectrophotometric Method.
   ABRAHAM M. RANDOLPH, M.D., New York, N. Y.
3. Cuvette Oximetry.
   WM. SUTTERER, M.D., Rochester, Minn. and EARL H. WOOD, M.D., Rochester, Minn.
4. Oxygen Tension by the Bubble Method.
   SOLBERT PERMUTT, M.D., Denver, Colo.
5. Polarography: Oxygen Electrode in Vitro.
   GEORGE POLGAR, M.D., Philadelphia, Pa.
6. Polarography: Oxygen Electrode in Vivo.
   SAMI SAID, M.D., Richmond, Va.
7. Gas Chromatography.
   JAY GOODKIND, M.D., New Haven, Conn.

Young Investigators' Award

Wednesday, May 17, 9:00 a.m.–12:00 p.m.

Presentations for the Young Investigators' Award of the American College of Cardiology.

First Scientific Session

Wednesday, May 17, 2:00–5:30 p.m.

Chairman: E. GREY DIMOND, M.D., President Elect.

1. President's Address.
   LOUIS F. BISHOP, M.D., President.
2. A New Method of Estimating Myocardial Blood Flow in Coronary Disease.
   WILLIAM HOLLANDER, M.D., IRVING M. MADOFF, M.D. and ARAM V. CHOBANIAN, Boston, Mass.
3. Measurements of the Total Coronary Blood Flow.
   DAVID W. IRVING, M.D. and ELIOT CORDAY, M.D., Los Angeles, Calif.
4. The Cerebral Circulation in Cardiovascular Disease.
   PAUL NOVACK, M.D., BERNARD GOLUBOFF, M.D., HENRY A. SHENKIN, M.D., FERNANDO A. MENDOZA, M.D., DIEGO DEARMAS, M.D., GIAMPIERO BARTOLUCCI, M.D. and AHMED USMAN, M.D., Philadelphia, Pa.
5. Problems in the Use and Evaluation of Measures to Lower Serum Cholesterol.
   MAURICE M. BEST, M.D. and CHARLES H. DUNCAN, M.D., Louisville, Ky.
6. The Practical Significance of the Radioactive Fat Tolerance Test and Its Relation to Current Therapy for Hypercholesterolemia.
   DONALD BERKOWITZ, M.D., JOHN J. SPITZER, M.D. and WILLIAM LIKOFF, M.D., Philadelphia, Pa.

Chairman: ROBERT LESLIE, M.D., Vice President.

7. Hypercholesterolemia, A Study in Its Etiology and Why It Is Influenced by Dietary Vegetable Oils.
   WALTER L. EVANS, M.D., WILLIAM B. RAWLS, M.D., CHARLES MISTRETTA, M.D., FRANK D'ALESSANDRO, M.D., DIONISIO CALOSA, M.D. and ELIAS TAWIL, M.D., New York, N. Y.
8. Dietary and Lipid Studies in Seventh-Day Adventists.
   RICHARD T. WALDEN, M.D., Loma Linda, Calif., ABRAHAM SUNSHINE, M.D., LOUIS E. SCHAEFER, M.D. and ERNEST WYNDER, M.D., New York, N. Y.
9. The Problem of Hidden Myocardial Infarction.
   STEPHEN R. ELEK, M.D., Los Angeles, Calif.
10. The Use of Steroids in Heart Block.
    MYRON PRINZMETAL, M.D. and REXFORD KENNAMER, M.D., Los Angeles, Calif.
11. Evaluation of Currently Used Agents in the Treatment of Angina Pectoris by Means of the Master Two-Step Test. Peritrate, Cardilate, Isordil, MAO Inhibitors and Mer-29.
    HENRY I. RUSSEK, M.D., Staten Island, N.Y.
12. Long Survival Following Myocardial Infarction. Report on 255 Patients Living Ten Years or Longer After the First Attack.
    LOUIS H. SIGLER, M.D., Brooklyn, N. Y.

Fireside Conferences

Wednesday, May 17, 8:30–10:30 p.m.

1. Arrhythmias and Their Management.
   SAMUEL BELLET, M.D., Moderator, Philadelphia, Pa., SIMON DACK, M.D., N.Y., N.Y. and GORDON K. MOE, M.D. Utica, N. Y.
2. The Present Status of Fibrinolysins in Practice.
   EUGENE E. CLIFFTON, M.D., Moderator, New York, N. Y., JULIAN AMBRUSE, M.D., Buffalo, N. Y., KENNETH M. MOSER, M.D., Washington, D. C. and IRWIN NYDICK, New York, N. Y.
3. The Management of Angina Pectoris.
   ELIOT CORDAY, M.D., Moderator, Los Angeles, Calif., FRANCIS CHAMBERLAIN, M.D., San Francisco, Calif., and RICHARD S. COSBY, M.D., Pasadena, Calif.
4. The Surgical Management of Extracranial Arterial Occlusive Disease.
   MICHAEL E. DEBAKEY, M.D., Houston, Texas and MILLER FISHER, M.D., Boston, Mass.
5. Problems in Vector-Electrocardiography.
   STEPHEN R. ELEK, M.D., Co-moderator, Los Angeles, Calif., ARTHUR GRISHMAN, M.D., Co-moderator, New York, N. Y., JOHN A. OSBORNE, M.D., Vancouver, B. C. and THOMAS J. WALSH, M.D., St. Louis, Mo.
6. Anticoagulant Therapy in Thrombo-Embolic Disease States.
   WILLIAM T. FOLEY, M.D., Moderator, New York, N. Y., E. STERLING NICHOL, M.D., Miami, Fla. and BENJAMIN MANCHESTER, M.D., Washington, D. C.
7. Advantages and Disadvantages in the Surgical Treatment of Coronary Artery Disease.
   DWIGHT E. HARKEN, M.D., Moderator, Boston, Mass., RICHARD GORLIN, M.D., Boston, Mass., WILLIAM LIKOFF, M.D., Philadelphia, Pa. and F. MASON SONES, JR., M.D., Cleveland, Ohio.
8. Problems in Electrocardiography.
   IRWIN HOFFMAN, M.D., Moderator, Los Angeles, Calif., J. RODERICK KITCHELL, M.D., Philadelphia, Pa. and JOSEPH E. F. RISEMAN, M.D., Boston, Mass.
9. Problems in Cardiovascular Roentgenology.
   GEORGE JACOBSON, M.D., Moderator, Los Angeles, Calif., JOHN A. EVANS, M.D., New York, N. Y., MELVIN M. FIGLEY, M.D., Seattle, Wash. and JOHN KIRKPATRICK, JR., M.D., Philadelphia, Pa.
10. Practical Problems in Open Heart Surgery and the Surgical Treatment of Acquired and Congenital Heart Lesions Using Open Technics.
    JEROME H. KAY, M.D., Moderator, Los Angeles, Calif., ROBERT GROSS, M.D., Boston, Mass. and CHARLES P. BAILEY, M.D., New York, N. Y.
11. Recognition and Management of Congenital Defects in the First Year of Life.
    JOHN D. KEITH, M.D., Moderator, Toronto, Ontario, J. FRANK DAMMANN, JR., M.D., Charlottesville, Va., MARY ALLEN ENGLE, M.D., New York, N. Y., EDWARD C. LAMBERT, M.D., Buffalo, N. Y., JAMES MANNING, M.D., Rochester, N. Y., ALEXANDER S. NADAS, M.D., Boston, Mass. and P. A. ONGLEY, M.D., Rochester, Minn.
12. Problems in Electrocardiography.
    E. LEPESCHKIN, M.D., Moderator, Burlington, Vt., ARTHUR M. MASTER, M.D., New York, N. Y., DAVID SCHERF, M.D., New York, N. Y. and ROBERT F. ZIEGLER, M.D., Detroit Mich.
13. The Evaluation of the Rheumatic Fever Suspect.
    BENEDICT F. MASSELL, M.D., Moderator, Boston, Mass., EDWARD E. FISCHEL, M.D., New York, N. Y., MILTON SASLAW, M.D., Miami, Fla. and JACK A. SHEINKOPF, M.D., Beverly Hills, Calif.
14. The Edematous States, Their Management.
    JOHN H. MOYER, M.D., Moderator, Philadelphia, Pa., ALBERT BREST, M.D., Philadelphia, Pa., RAY W. GIFFORD, JR., M.D., Rochester, Minn. and SIR F. HORACE SMIRK, M.D., Dunedin, New Zealand.
15. Monoamine Oxidase Inhibitors.
    ROBERT W. OBLATH, M.D., Moderator, Sherman Oaks, Calif., WILLIAM HOLLANDER, M.D., Boston, Mass., HENRY I. RUSSEK, M.D., Staten Island, N. Y., ARTHUR L. SCHERBEL, M.D., Cleveland, Ohio and GERHARD ZBINDEN, M.D., Nutley, N. J.
16. The Role of the Catecholamines in Cardiovascular Diseases.
    WILHELM RAAB, M.D., Moderator, Burlington, Vt., J. E. SZACKAS, M.D., Bethesda, Md., A. C. WIGMAN, M.D., Detroit, Mich., MORTON D. BOGDONOFF, M.D., Durham, N. C. and ALBERT J. PLUMMER, M.D., Summit, N. J.
17. Does Stress Play a Role in Atherogenesis?
    RAY H. ROSENMAN, M.D., Moderator, San Francisco, Calif., CHESTERFIELD G. GUNN, M.D., Oklahoma City, Okla. and REUBEN STRAUS, M.D., Burbank, Calif.
18. The Problems in Digitalis Administration.
    JOHN J. SAMPSON, M.D., Moderator, San

Francisco, Calif., CHARLES K. FRIEDBERG, M.D., New York, N. Y. and BERNARD LOWN, M.D., Boston, Mass.

19. Adaptation of Cardiovascular Function to Hot and Cold Environments.
    KARL E. SCHAEFER, M.D., Moderator, New London, Conn., DAVID E. BASS, M.D., Natick, Mass., AUSTIN HENSCHEL, M.D., Natick, Mass., THOMAS F. HORNBEIN, M.D., St. Louis, Mo. and DUANE E. GRAVELINE, M.D., Wright-Patterson AFB, Ohio.
20. Serum Triglyceride Levels in Man in Health and Disease.
    LOUIS E. SCHAEFER, M.D., Moderator, New York, N. Y., JULES HIRSCH, M.D., New York, N. Y. and KURT HIRSCHHORN, M.D., New York, N. Y.
21. Congenital Defects Involving the Great Vessels.
    HELEN B. TAUSSIG, M.D., Baltimore, Md. and DENTON A. COOLEY, M.D., Houston, Texas.
22. Peripheral Vascular Problems.
    TRAVIS WINSOR, M.D., Moderator, Los Angeles, Calif., DAVID ABRAMSON, M.D., Chicago, Ill. and CHESTER HYMAN, M.D., Los Angeles, Calif.
23. The Management of Cerebral Vascular Disease.
    IRVING S. WRIGHT, M.D., Moderator, New York, N. Y., SIGMUND GROCH, M.D., New York, N. Y. and ROBERT G. SIEKERT, M.D., Rochester, Minn.
24. Hypothermia.
    W. GLENN YOUNG, JR., M.D., Moderator, Durham, N. C., WALTER L. FLOYD, M.D., Durham, N. C., ARCHER S. GORDON, M.D., Los Angeles, Calif. and JOHN Y. TEMPLETON, III, M.D., Philadelphia, Pa.
25. Mechanisms of Syncope.
    WILLARD J. ZINN, M.D., Moderator, Los Angeles, Calif., GEORGE DERMSKIAN, M.D., New York, N. Y., WILLIAM C. GIBSON, M.D., Vancouver, B. C., ROGER B. HICKLER, M.D., Boston, Mass. and JOHN B. SCHWEDEL, M.D., New York, N. Y.

Second Scientific Session

Thursday, May 18, 9:00–11:30 a.m.

SYMPOSIUM ON AORTIC VALVE

Chairman: CHARLES A. HUFNAGEL, M.D.

1. Congenital Bicuspid Aortic Valve. The Natural History of Nine Cases.
    MATTHEW J. FERGUSON, M.D. and Sister MICHAEL MARIE O'BRIEN, M.D., New York, N. Y.
2. A Critical Review of Aortic Stenosis.
    RICHARD S. COSBY, M.D., BALAKRISHA HEGDE, M.D. and MARY MAYO, M.D., Los Angeles, Calif.
3. The Surgical Problems of Congenital Aortic Stenosis.
    BERT W. MEYER, M.D., Los Angeles, Calif.
4. Experimental and Clinical Experiences with the Bicuspid Operation for Aortic Insufficiency.
    JOSEPH J. GARAMELLA, M.D., W. ROBERT SCHMIDT, M.D. and NATHAN KENNETH JENSON, M.D., Minneapolis, Minn.
5. The Surgical Treatment of Aortic Regurgitation by Valvular Prostheses.
    EARLE B. KAY, M.D., DAVID MENDELSOHN, M.D. and HENRY A. ZIMMERMAN, M.D., Cleveland, Ohio.
6. Partial and Complete Aortic and Mitral Valve Prostheses.
    DWIGHT E. HARKEN, M.D., WARREN J. TAYLOR, M.D., ARMAND A. LEFEMINE, M.D., STEVEN LUNZER, M.D., HENRY B. C. LOW, M.D., MANFRED L. COHEN, M.D. and ANNA M. FOSBERG, M.D., Boston, Mass.
7. Open Heart Treatment of Mitral Insufficiency and Combined Mitral Stenosis and Insufficiency.
    JEROME H. KAY, M.D. and OSCAR MAGIDSON, M.D., Los Angeles, Calif.
8. Reconstructive Methods for Aortic Valvular Disease.
    CHARLES A. HUFNAGEL, M.D., PETER W. CONRAD, M.D., ROQUE PIFARRE, M.D. and NESTER DE VENECIA, M.D., Washington, D.C.

Panel Discussion by All Essayists

Third Scientific Session

Thursday, May 18, 11:30 a.m.–12:30 p.m., 2:00–4:30 p.m.

SYMPOSIUM ON HYPERTENSION

Chairman: JOHN H. MOYER, M.D.

CONVENTION GUEST LECTURE

Introduction: GEORGE C. GRIFFITH, M.D.

Some Principles of Hypotensive Therapy Considered in Relationship to the Pathogenesis of Essential Hypertension.
SIR F. HORACE SMIRK, M.D., F.R.C.P., Dunedin, New Zealand.

1. Mechanisms in Essential Hypertension.
    MILTON MENDLOWITZ, M.D., STANLEY E. GITLOW, M.D., ROBERT L. WOLF, M.D. and NOSRAT NAFTCHI, M.D., New York, N. Y.
2. Pharmacodynamics and Clinical Use of

Three Drugs Which Block Sympathetic Neural Activity.
WALTER M. KIRKENDALL, M.D., Iowa City, Iowa.

3. Decarboxylase Inhibitors in the Treatment of Hypertension.
ALBERT BREST, M.D., Philadelphia, Pa.
4. Reversible Renal Hypertension. Clinical Characteristics and Predictive Tests.
MORTON H. MAXWELL, M.D., Los Angeles, Calif.
5. Pheochromocytoma.
VARNER J. JOHNS, JR., M.D., Los Angeles, Calif.
6. Flexibility in Drug Treatment of Essential Hypertension.
ROBERT W. WILKINS, M.D., Boston, Mass.
7. The Isotope Renogram, Differential Renal-Function Study and Aorto-Renal Arteriogram in the Clinical Evaluation of Hypertensive Patients.
RAY W. GIFFORD, JR., M.D. and JAMES C. HUNT, M.D., Rochester, Minn.
8. Diagnosis and Treatment of Renovascular Hypertension.
GEORGE C. MORRIS, JR., M.D., Houston, Texas.

Panel Discussion by All Essayists

Annual Business Meeting
Thursday, May 18, 4:30–5:30 p.m.

Fourth Scientific Session
Friday, May 19, 9:00 a.m.–12:30 p.m.

SYMPOSIUM ON
THE EVALUATION OF FIBRINOLYTIC AGENTS IN THE TREATMENT OF CARDIOVASCULAR DISEASE

Chairman: JOHN S. LA DUE, M.D., Secretary

1. Studies in Experimental Myocardial Infarction.
PAUL RUEGSEGGER, M.D., New York, N. Y.
2. Technics of Treatment.
ALAN JOHNSON, M.D., New York, N. Y.
3. Experiences in Peripheral Vascular Disease.
EUGENE E. CLIFFTON, M.D., New York, N.Y.
4. Clinical Evaluation in Acute Myocardial Infarction.
ISAAC H. RICHTER, M.D., New York, N. Y.

Panel Discussion

Chairman: C. WALTON LILLEHEI, M.D., Vice President

5. Cardiac Metabolism.
RICHARD J. BING, M.D., Detroit, Mich.
6. New Methods and Technics in Cardiovascular Roentgenology.
GEORGE JACOBSON, M.D., Moderator, Los Angeles, Calif., JOHN A. EVANS, M.D., New York, N. Y., MELVIN M. FIGLEY, M.D., Seattle, Wash. and JOHN KIRKPATRICK, JR., M.D., Philadelphia, Pa.

Fifth Scientific Session
Friday, May 19, 2:00–5:30 p.m.

Chairman: IRVING BROTMAN, M.D., Assistant Secretary

1. The Hydrogen-Platinum Electrode System in Detection of Cardiac Shunts.
EDWARD S. HYMAN, M.D., ALBERT L. HYMAN, M.D., KENNETH HYATT, M.D. and WILLIAM MYERS, M.D., New Orleans La.
2. Observations on the Use of Externally Monitored Radioisotopes in Measuring Coronary Blood Flow.
SYLVAN L. WEINBERG, M.D., G. RICHARD GROVE, M.D., CEMAL M. CAGIRGAN, M.D. and WARREN BLANCHARD, M.D., Dayton, Ohio.
3. Assisted Circulation in Acute Coronary Occlusion. I. Production of Acute Myocardial Infarction with Graded Doses of Plastic Microspheres.
JOHN A. JACOBY, M.D., WARREN J. TAYLOR, M.D., GEORGE T. SMITH, M.D., RICHARD GORLIN, M.D. and DWIGHT E. HARKEN, M.D., Boston, Mass.
4. Prolonged Mechanical Assistance in Left-Sided Heart Failure.
CHARLES P. BAILEY, M.D., ROBERT A. O'CONNOR, M.D., ABRAHAM SCHAFFER, M.D., TERUO HIROSE, M.D. and PHOTOS PANAGOPOULOS, M.D., New York, N. Y.
5. Timing of Vibrocardiographic Wave Intervals to Detect Coronary Insufficiency.
CLARENCE M. AGRESS, M.D., STANLEY WEGNER, M.D. and ROBERT M. MULLER, M.D., Los Angeles, Calif.
6. High Frequency Phonocardiography.
ALDO A. LUISADA, M.D. and GIULIANO DI BARTOLO, M.D., Chicago, Ill.
7. The Role of Intracardiac Phonocardiography in the Differential Diagnosis of Continuous Precordial Murmurs.
HOWARD F. WARNER, M.D., ABDOL-NABI MOGHADAM, M.D., JEROME A. HUBSHER, M.D., JOHN D. WALLACE, M.D. and DAVID H. LEWIS, M.D., Philadelphia, Pa.
8. Direct Studies of the Activation of the Purkinje System Before and After Left Bundle Branch Block.
ROBERT S. VENEROSE, M.D., JACKSON H. STUCKEY, M.D., BRIAN F. HOFFMAN, M.D.

and MARTIN SEIDENSTEIN, M.D., Brooklyn, N. Y.

9. Myocardial Hypoxia Elicited by Neurogenic and Blood-borne Catecholamines During Impairment of Coronary Dilatability.
   WILHELM RAAB, M.D., E. LEPESCHKIN, M.D., PAUL VAN LITH, M.D. and H. C. HERRLICH, M.D., Burlington, Vt.
10. The Relationship Between Coronary Blood Flow, Myocardial Oxygen Consumption and Cardiac Work as Influenced by Pharmacologic Agents.
    VERNON E. WENDT, M.D., JOHN F. SUNDERMEYER, M.D., P. B. DEN BAKKER, M.D. and RICHARD J. BING, M.D., Detroit, Mich.
11. The Hemodynamic Effects of Prolonged Hypothermia Combined with Closed-Chest Extracorporeal Circulation in Experimental Myocardial Infarction with Shock.
    LESLIE A. KUHN, M.D., FRANK M. WEISER, M.D., A. ROBERT BECK, M.D., JOHN D'ARIA, M.D. and IRWIN KRASNA, M.D., New York, N. Y.
12. Treatment of Heart Block and Adams-Stokes Syndrome With Oral Sustained-Action Isoproterenol.
    SIMON DACK, M.D. and STANLEY R. ROBBIN, M.D., New York, N. Y.

Groedel Memorial Lecture on Humanities in Medicine

Friday evening, May 19, 8:00 p.m.

The Medical and Scientific Significance of the Seemingly Small, Trivial and Insignificant.
WILLIAM B. BEAN, M.D., Iowa City, Iowa.

Sixth Scientific Session

Saturday, May 20, 9:00 a.m.–12:30 p.m.

Chairman: ALDO A. LUISADA, M.D., Trustee.

1. Physiologic Aspects of Hemangioblastic Tissues.
   SIMON RODBARD, M.D. and BARBARA HOWELL, M.D., Buffalo, N. Y.
2. The Role of Isopropylnorepinephrine in the Treatment of Digitalis Intoxication.
   DAVID J. BAKER, M.D., PAUL M. NONKIN, M.D., MARTIN S. STERNBERG, M.D. and FRED WASSERMAN, M.D., Coral Gables, Fla.
3. The Combined Use of Dihydroergocornine Methane Sulphonate (DHO-180) and Phenylindandione (Hedulin) in the Treatment of Acute Cerebral Thrombosis. A Preliminary Study.
   RALPH M. TANDOWSKY, M.D., Hollywood, Calif.
4. Sodium D-Thyroxine in the Therapy of Hypercholesterolemia of Coronary Artery Disease.
   SHELDON R. BENDER, M.D., Philadelphia, Pa.
5. The Rib Syndrome.
   MAURICE S. RAWLINGS, M.D., Chattanooga, Tenn.
6. The Use of Long Term Anticoagulant Therapy in Private Practice for Coronary Heart Disease.
   W. T. MCCOLLUM, M.D., KENT ALEXANDER, M.D., ARTHUR E. SCHMIDT, M.D., GERALD HONICK, M.D. and LEO WADE, M.D., Oklahoma City, Okla.

Chairman: I. FRANK TULLIS, M.D., Trustee

7. Causes of Pulmonary Artery Stenosis—Intra- and Extra-Luminal.
   DAVID C. LEVINSON, M.D. and RONALD DANZIG, M.D., Los Angeles, Calif.
8. Aortico-Pulmonary Septal Defect.
   HENRY N. NEUFELD, M.D., RICHARD G. LESTER, M.D., RAY C. ANDERSON, M.D., PAUL ADAMS, JR., M.D., C. WALTON LILLEHEI, M.D. and JESSE E. EDWARDS, M.D., Minneapolis, Minn.
9. The Differential Diagnosis of Patent Ductus Arteriosus and Ventricular Septal Defect in Infancy.
   ABDOL-NABI MOGHADAM, M.D., JEROME A. HUBSHER, M.D., HOWARD F. WARNER, M.D., JOHN D. WALLACE, M.D. and DAVID H. LEWIS, M.D., Philadelphia, Pa.
10. Patent Ductus Arteriosus as a Cause of Congestive Heart Failure in the First Year of Life.
    MARTIN J. FRANK, M.D., JOHN D. MCGINTY, M.D., TIMOTHY J. REGAN, M.D., PRESCOTT JORDAN, JR., M.D. and HARPER K. HELLEMS, M.D., Jersey City, N. J. and Detroit, Mich.
11. Acute Effects of Triparanol Therapy.
    DAVID H. BLANKENHORN, M.D. and OLIVER T. KUZMA, M.D., Los Angeles, Calif.
12. Urine Glutamic Oxalacetic Transaminase Activity in Acute Myocardial Infarction.
    ROBERT B. KALMANSOHN, M.D. and RICHARD W. KALMANSOHN, M.D., Los Angeles, Calif.
13. Alterations of Indices of Liver Function in Congestive Heart Failure with Particular Reference to Serum Enzymes.
    SIDNEY M. RICHMAN, M.D., ABNER DELMAN, M.D. and DAVID GROB, M.D., Brooklyn, N. Y.

"First in the hearts"
of cardiac patients

A.C.M.I.
CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States – originally for ureteral use – later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill – all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

Nylon woven cardiac catheters

A.C.M.I. TRADE MARK

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY, PELHAM MANOR, N. Y.

Photo courtesy Methodist Hospital, Rochester, Minnesota

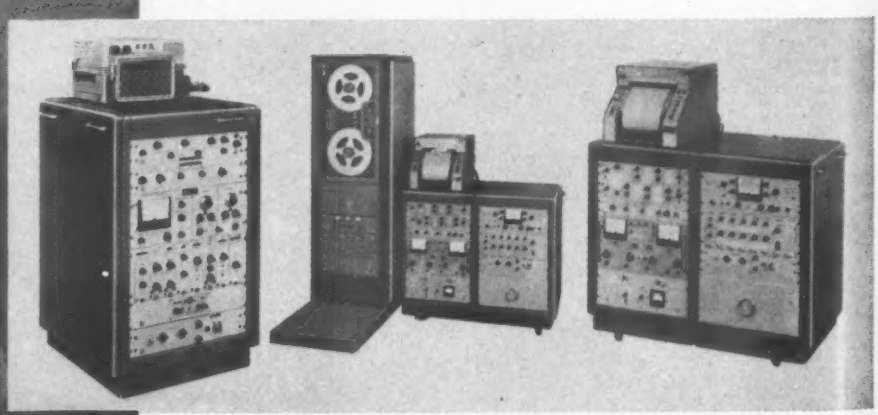
NEW FROM HONEYWELL...

Electronic medical instrumentation

Now available from Honeywell — a world leader in the field of precision electronic equipment — is a complete line of medical instrumentation designed to greatly improve your capabilities for measuring and recording physiological functions. Currently in production are coordinated systems for the following measurements:

Body temperatures • Respiration rate, flow, and volume • Chest expansion • Blood dye curve measurements • Phonocardiography (PCG) • Pulse rate • Electromyography (EMG) • Nerve potentials • Electroencephalography (EEG) • O_2 content of blood (Oximetry) • Skin temperatures • Electrocardiography (EKG) • Pressures — stomach, intestinal, muscular, uterine • Dynamic blood pressures (arterial and venous) • Ballistocardiography (BCG).

When you order a Honeywell Electronic Medical System, you get more than just components — you get a complete, integrated system, ready to plug in and use. In addition, your purchase includes an interest by Honeywell which extends beyond the sale to successful operation. Honeywell branch offices — from coast to coast, across Canada, and around the world — are staffed with skilled technicians, equipped to make emergency repairs or render periodic service to your system.

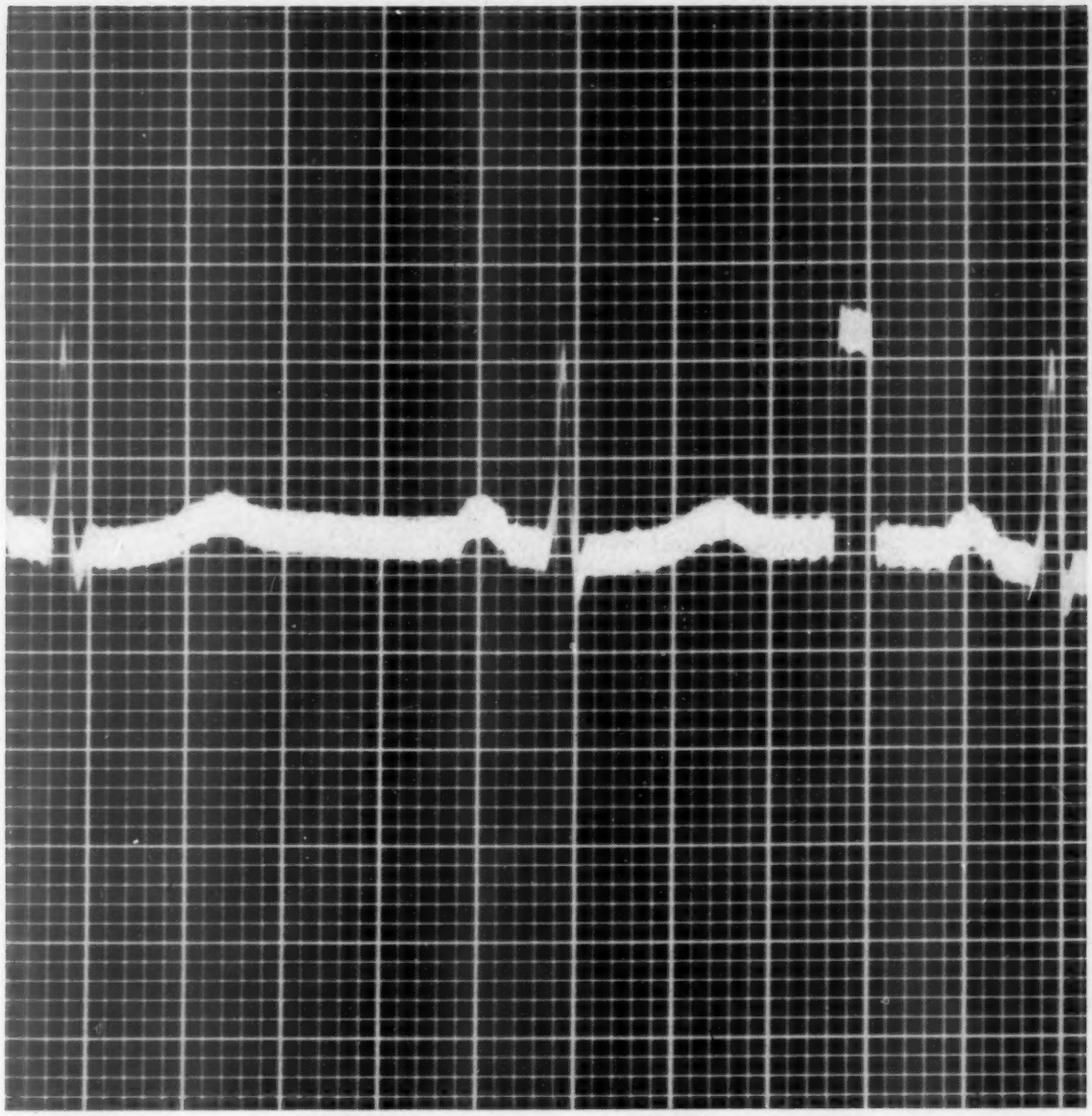


For further information and assistance in determining which Honeywell Electronic Medical System will best fill your requirements, please contact:

Minneapolis-Honeywell, Heiland Division
5200 E. Evans Ave., Denver 22, Colorado

Honeywell

Electronic Medical Systems



Your Heart Patient

–and a natural way to meet his need for milk's nutrition
–without risking the penalties of fat

Although your heart patients need the vital nutrition of milk, often the calories and saturated fat both pose problems.

Now there's a fresh-flavor, delicious, and *natural* way to help assure your patients' good nutritional status. Today, Carnation Instant Nonfat Dry Milk provides all the protein, calcium, and B-vitamins of fresh, whole milk – but without the fat.

And Carnation Instant can be mixed 25% over-strength to provide more calcium, protein, and B-vitamins than ordinary nonfat milk. ⅓ cup extra crystals per liquid quart gives patients 25% more needed nutrition—*without* excessive calories. It tastes delicious, with a richer flavor they'll enjoy. Even enriched, it costs them only 12¢ a quart.

ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

An instructive new seminar

that presents recent clinical findings on

MYCOTIC INFECTIONS

This seminar contains:

Current Concepts of Diagnostic Serology and Skin Hypersensitivity in the Mycoses.

S. B. SALVIN, PH.D., *Hamilton, Montana.*

From the U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Institutes of Allergy and Infectious Diseases, Rocky Mountain Laboratory, Hamilton, Montana.

The Course and Prognosis of Histoplasmosis.

HARRY RUBIN, M.D., MICHAEL L. FURCOLOW, M.D., *Kansas City, Kansas,* J. LEWIS YATES, M.D. and CHARLES A. BRASHER, M.D., *Mount Vernon, Missouri.*

From the Kansas City Field Station, Communicable Disease Center, Bureau of State Services, Public Health Service, U.S. Department of Health, Education, and Welfare, University of Kansas School of Medicine, Kansas City, Kansas, and the Missouri State Sanatorium, Mount Vernon, Missouri.

Aspergillosis. A Review and Report of Twelve Cases.

SYDNEY M. FINEGOLD, M.D., DRAKE WILL, M.D. and JOHN F. MURRAY, M.D., *Los Angeles, California.*

From the Department of Medicine, Wadsworth Hospital, Veterans Administration Center, Los Angeles, and Department of Medicine and Pathology, University of California Medical Center, Los Angeles, California.

The Use of Amphotericin B in the Treatment of Coccidioidal Disease.

WILLIAM A. WINN, M.D., *Springville, California.*

From the Department of Medicine, Tulare-Kings Counties Hospital, Springville, California.

North American Blastomycosis.

E. RICHARD HARRELL, M.D. and ARTHUR C. CURTIS, M.D., *Ann Arbor, Michigan.*

From the Department of Dermatology, University of Michigan Medical Center, and the V.A. Hospital, Ann Arbor, Michigan.

Cryptococcosis (Torulosis). Current Concepts and Therapy.

M. L. LITTMAN, M.D., PH.D., *New York, New York.*

From the Departments of Microbiology and Medicine, the Mount Sinai Hospital, New York, N. Y. These studies were supported in part by research grants from the Squibb Institute for Medical Research and the National Science Foundation.

Actinomycosis and Nocardiosis. A Review of Basic Differences in Therapy.

JOSPEH W. PEABODY, JR., M.D., *Washington, D.C.,* and JOHN H. SEABURY, M.D., *New Orleans, Louisiana.*

[*Fully illustrated—Many references included*]

The Seminar on Mycotic Infections originally appeared in The American Journal of Medicine and is now available in bound library reference form at $3.00 per copy.

THE AMERICAN JOURNAL OF MEDICINE

466 Lexington Avenue • New York 17, N. Y.

COUMADIN®

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

the proven anticoagulant for long-term maintenance

now more widely prescribed than all other oral anticoagulants combined

152,000,000

Over ~~131,000,000~~ doses administered to date

Over 125 published papers since 1953

Endo

the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.[1,2]

1. Boor, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., May, 1960, p. 13.

Full range of oral and parenteral dosage forms—COUMADIN* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

*Manufactured under license from the Wisconsin Alumni Research Foundation.

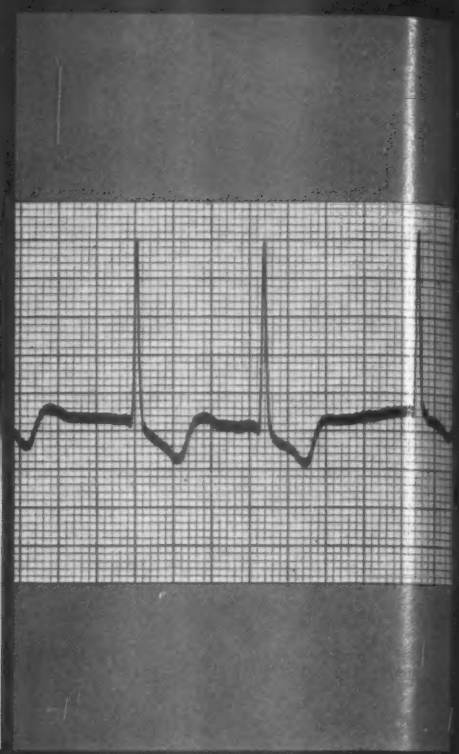
Complete Information and Reprints on Request

ENDO LABORATORIES Richmond Hill 18, New York

*before treatment**

Hypertensive cardiovascular disease, Grade IV D (New York Heart Assn. classification). 52 year old female with atrial fibrillation, receiving maintenance dosage of digitalis.

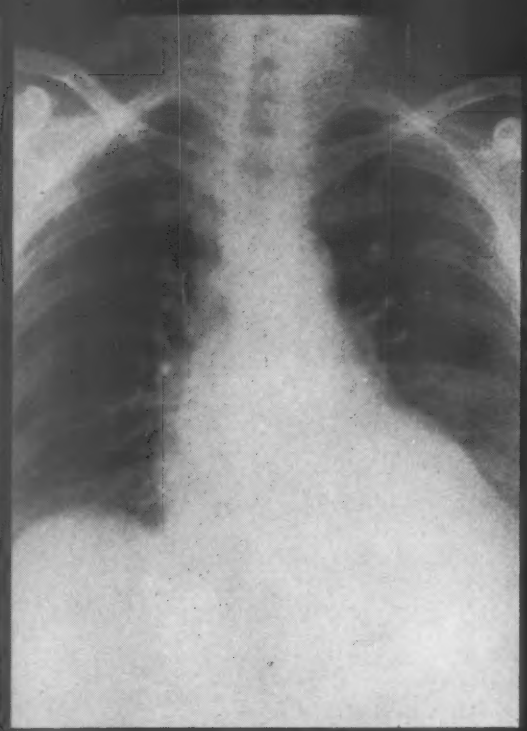
Cardiac enlargement and pulmonary congestion.



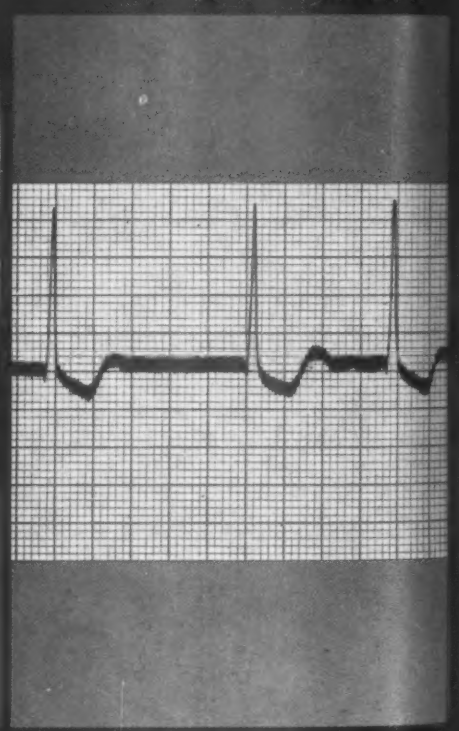
Left ventricular strain and hypertrophy (ST depression in Lead V4).

after one month on HYDROPRES*

Alternating daily dosage of 1 to 2 HYDROPRES-50 Tablets.



Reduction in heart size and clearing of congestion.



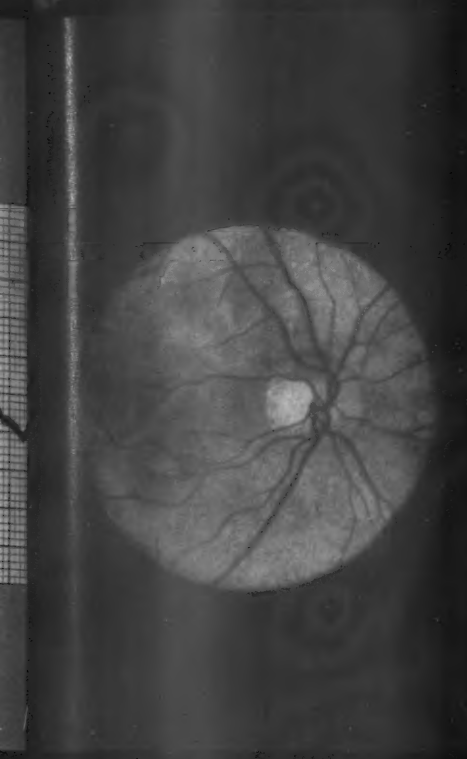
Changes toward normal (less ST depression).

*case report

effective by itself in many hypertensives...
indicated in all degrees of hypertension

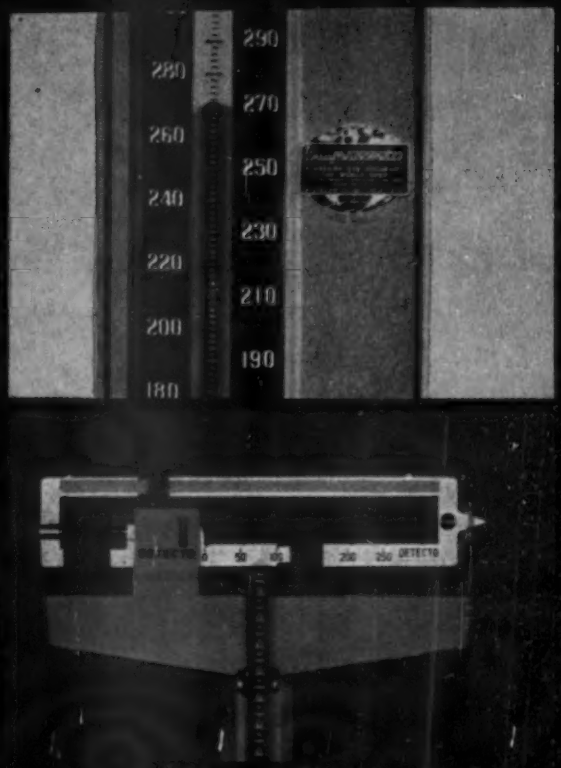
HYDROPRES®

HYDRODIURIL® with RESERPINE
HYDROCHLOROTHIAZIDE

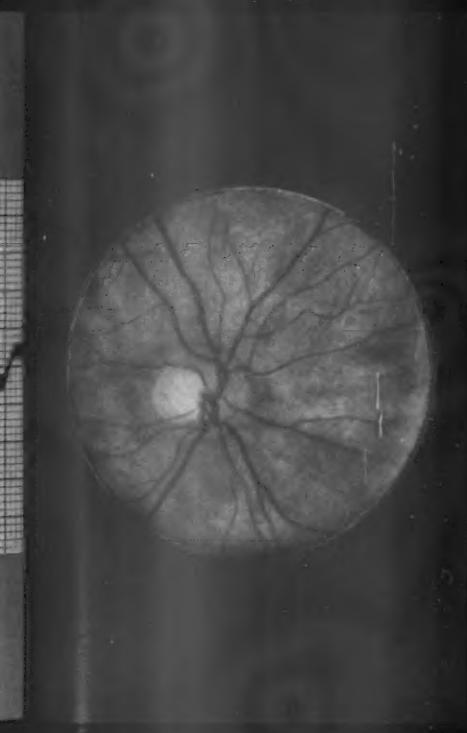


Hypertensive retinopathy with hemorrhages.

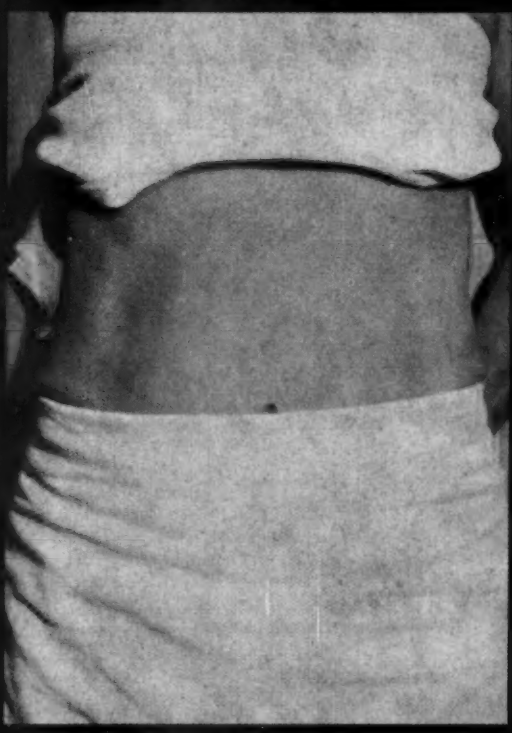
Liver palpable 5 fingerbreadths below costal margin.



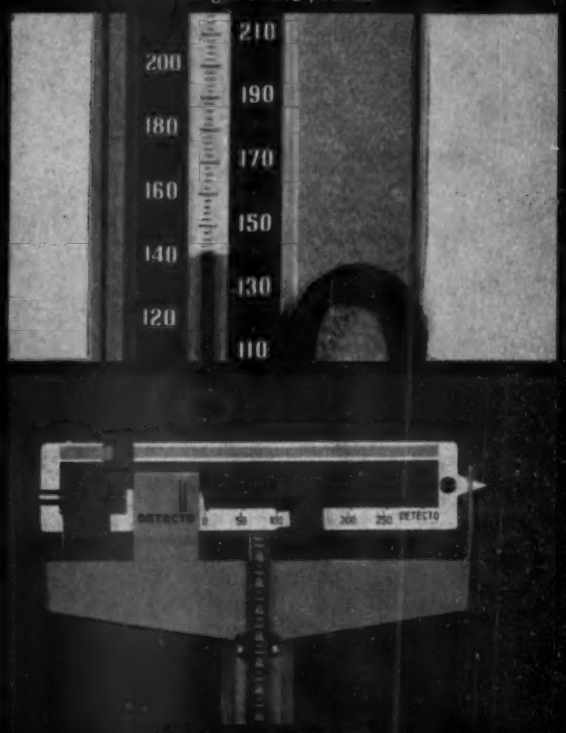
Blood pressure 270/120.
Weight 110½ pounds.



Very little change.



Liver not palpable.



Blood pressure 140/72.
Weight 105 pounds.

HYDROPRES-25

25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to four times a day.

HYDROPRES-50

50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine per tablet. One tablet one or two times a day.

also available:

HYDROPRES-Ka†25

25 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

HYDROPRES-Ka†50

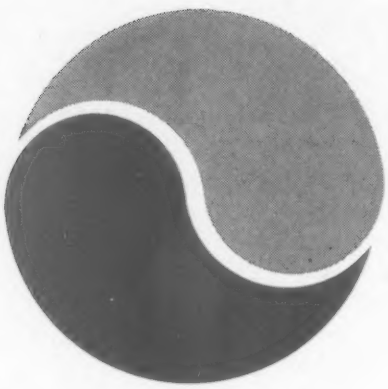
50 mg. HydroDIURIL hydrochlorothiazide, 0.125 mg. reserpine, 572 mg. potassium chloride (equivalent to 300 mg. potassium) per tablet.

It is essential to reduce the dosage of other antihypertensive agents, particularly the ganglion blockers, by at least 50 per cent immediately upon addition of these agents or of HYDROPRES Tablets to the regimen.

Before prescribing or administering HYDROPRES, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

†HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.



essential
partners
in the
control
of edema

classic MERCUHYDRIN®

brand of meralluride sodium

nonmercurial METAHYDRIN®

brand of trichlormethiazide

Now...the alternate or combined use of these two drugs can help the physician meet with maximum efficiency the demands of diuretic therapy in almost any phase or degree of cardiac edema—acute or chronic.

SEND FOR METAHYDRIN BROCHURE

SUPPLIED:

METAHYDRIN—Tablets of 2 mg. and 4 mg. in bottles of 100 and 1000.

MERCUHYDRIN—1 cc. and 2 cc. ampuls in boxes of 12, 25 and 100, and 10 cc. rubber capped, multiple dose vials in boxes of 6, 25 and 100.
Needs no refrigeration.

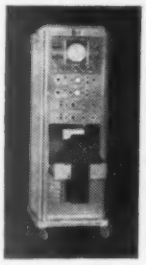
LAKESIDE

CAMBRIDGE CARDIAC DIAGNOSTIC INSTRUMENTS

"Versa-Scribe"
The Versatile Electrocardiograph

The completely new portable instrument providing greatly improved performance and versatility not found in any other direct writing electrocardiograph. Small size (5¼" x 10½" x 17") and low weight—20 pounds.

Multi-Channel Recorders



For physiological research, cardiac catheterization and routine electrocardiography. Versatile and comprehensive, this series of new multi-channel recorders, when used with pertinent transducers, provides simultaneous indication and recording of EKGs, EEGs, stethograms and many other physiological phenomena. Various combinations of these functions can be traced simultaneously on a single record. Available in Photographic Recording and Direct Writing models.

ASSURE THE DOCTOR OF

Universally Accepted Records
Fundamental Accuracy
Lifetime Dependability
Minimum Maintenance Expense

Dye-Dilution Curve Recorder

Records changes of concentration of a dye injected at selected sites in the venous circulation. Determines cardiac output; detects and locates cardiac shunts.

Operating Room Cardioscope

Provides continuous observation of the Electrocardiogram and heart-rate during surgery. Warns of approaching cardiac stand-still. Explosion-proof. This cardioscope is a "must" for the modern Operating Room.

"Simpli-Scribe"
Direct Writer Electrocardiograph

Provides the Cardiologist, Clinic or Hospital with a portable direct writing Electrocardiograph of utmost usefulness and accuracy. Size 10⅜" x 10⅜" x 11"; weight 28 pounds, complete with all accessories.

Audio-Visual Heart Sound Recorder

Enables the Doctor to simultaneously HEAR, SEE and permanently RECORD heart sounds. Any portion of the heart sounds may be permanently recorded upon magnetic discs, which may then be played back and viewed at any time. When used in combination with the "Versa-Scribe" or "Simpli-Scribe" Electrocardiograph, the electrocardiogram may be viewed upon the cathode-ray screen of the Recorder while listening to the heart sounds.

CAMBRIDGE ALSO MAKES

EDUCATIONAL CARDIOSCOPE—For teaching electrocardiography and auscultation by audio-visual demonstration. The EKG, heart sounds and other physiological phenomena may be shown continuously on the 17-inch oscillograph screen. A tape recorder provides a permanent record of heart sounds which may be played back at any time for visual and audio demonstration in lieu of patients.

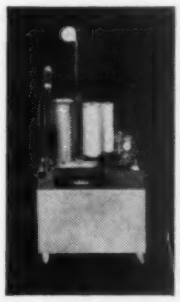
PLETHYSMOGRAPH—Records variations in volume of extremities as determined by the state of fullness of the blood vessels.

ELECTROKYMOGRAPH—Produces a continuous record of heart border motion at chosen points along the cardiac silhouette.

RESEARCH pH METER—For biological and research work. Sensitive to .005 pH, readings reproducible to .01 pH.

HUXLEY ULTRA MICROTOME—For cutting sections with exceptional uniformity between thicknesses of 100°A and 1500°A, in 50°A steps, for use with the electron microscope.

POCKET DOSIMETERS AND LINDEMANN-RYERSON ELECTROMETERS—For measurement of radioactive emission.



Pulmonary Function Tester

A completely integrated, easy-to-use instrument for the determination of such functions as Functional Residual Capacity, Tidal Volume, Vital Capacity, Total Lung Capacity, Total Breathing Capacity, Basal Metabolic Rate, etc.

Send for Descriptive Literature

SEE US AT BOOTH 55

CAMBRIDGE INSTRUMENT CO., INC.

Graybar Building, 420 Lexington Avenue, N. Y. 17, N. Y.

Cleveland 2, Ohio	Detroit 37, Mich.	Oak Park, Ill.	Jenkintown, Pa.	Silver Spring, Md.
8419 Lake Avenue	13730 W. Eight Mile Rd.	6605 West North Avenue	479 Old York Road	933 Gist Avenue

PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH

When the rhythm is wrong...PRONESTYL® HYDROCHLORIDE

Squibb Procainamide Hydrochloride

"Procaine amide [Pronestyl] should be [a] drug of choice in arrhythmias of ventricular origin."[1] "Pronestyl will be [a] drug of choice for intravenous use. The intramuscular preparation of Pronestyl has a clear advantage over the intramuscular preparation of quinidine because effects develop more rapidly."[2] Pronestyl sometimes stops arrhythmias which have not responded to quinidine[3, 4]. . . Pronestyl may be used in patients sensitive to quinidine . . . more prolonged action, less toxicity, less hypotensive effect than procaine . . . no CNS stimulation such as procaine may produce.

Supply: For convenient oral administration: Capsules, 0.25 Gm., in bottles of 100 and 1000. For I. M. and I. V. administration: Parenteral Solution, 100 mg. per cc., in vials of 10 cc. For full information see your Squibb Product Reference or Product Brief.

References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C. V. Mosby Co., St. Louis, 1950, p. 419. 3. Kayden, H. J., et al.: Med. Concepts Cardiovasc. Dis. 20:100, 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

SQUIBB *Squibb Quality – the Priceless Ingredient*

PRONESTYL® is a Squibb Trademark

NEW INSTRUMENTS FOR 1961...

featuring the

X-90A OXIMETER RECORDING SYSTEM

An oximeter system designed for recording blood oxygen saturation, and Evans Blue and Cardio-Green dye-dilution curves using the Waters oximeter earpiece and cuvette.

- **Immediate, continuous analysis**
- **High-performance recorder**
- **Simple, reliable operation**
- **Precision multi-turn controls**
- **Portable, rugged construction**

Write for Bulletin X-90/61

Factory trained representatives are located throughout the United States.

Waters | electro-medical instruments

THE WATERS CORPORATION

ROCHESTER, MINNESOTA

CHANGING YOUR ADDRESS?

Please fill out and return the coupon below:

THE AMERICAN JOURNAL OF CARDIOLOGY
Mailing Dept., 466 Lexington Avenue, New York 17, N. Y.

NAME_____
(please print)

NEW ADDRESS:

Street_____

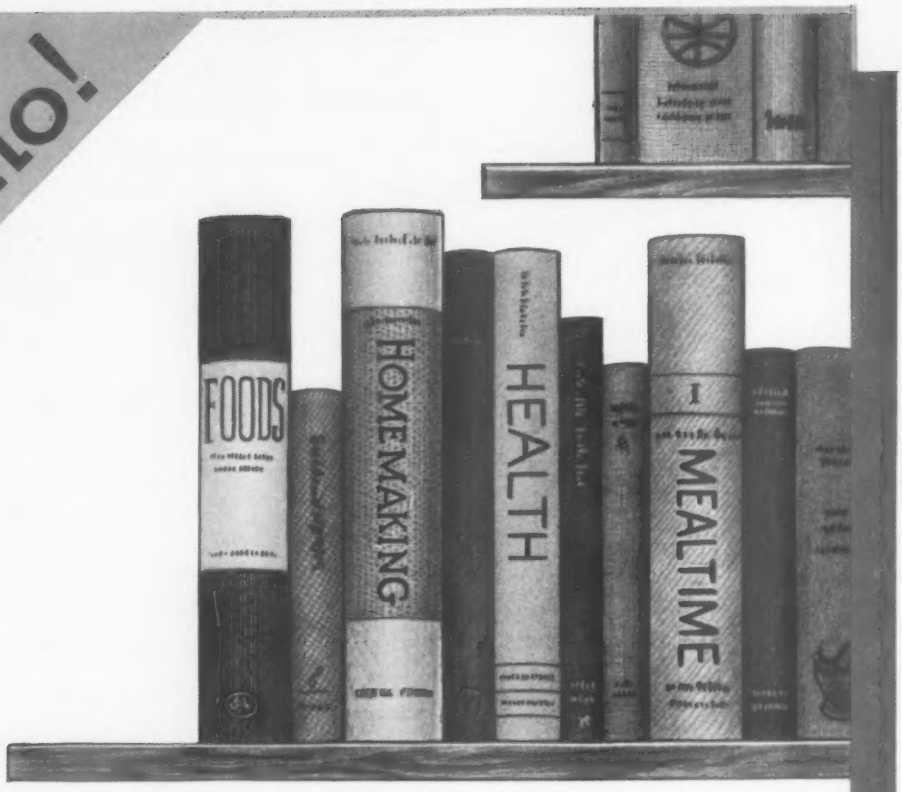
City_____ Zone_____ State_____

FORMER ADDRESS:

Street_____

City_____ Zone_____ State_____

memo!



Professional consultants recently examined 19 outstanding high school home economics and health textbooks and found that a basic cereal breakfast, among other breakfasts, appeared in every textbook examined. The majority of these textbooks included statements based on the Iowa Breakfast Studies.*

The need for a good breakfast every day is no longer a matter of opinion or personal preference. It is a scientific fact as demonstrated by the Iowa Breakfast Studies conducted by the College of Medicine at the State University of Iowa over the past decade.

**A Summary of the Iowa Breakfast Studies, published by Cereal Institute, Inc., May 1, 1957.*

CEREAL INSTITUTE, INC.
135 South La Salle Street, Chicago 3

A research and educational endeavor devoted to the betterment of national nutrition

cereals are low in fat

DRAMATIC
physical and emotional relief in
ANGINA PECTORIS

'round-the-clock protection against both pain and fear

COROVAS

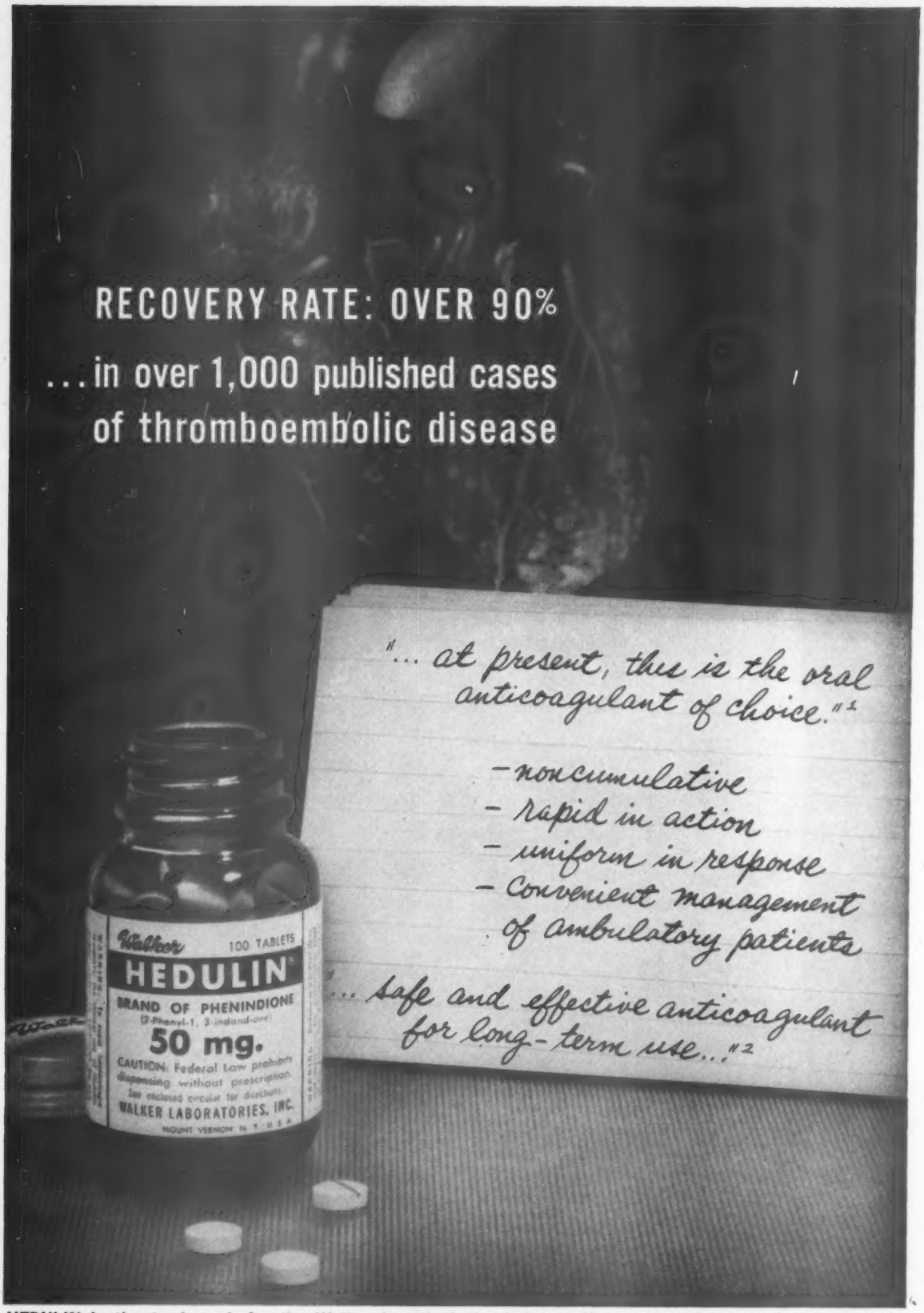
Tymcaps

COROVAS is a nontoxic, uniform-acting, long-acting vasodilator to control or prevent attacks of angina pectoris. One COROVAS Tymcap upon arising provides up to 12 hours of continuous coronary vasodilation, and another COROVAS Tymcap before the evening meal affords maximum protection against seizures all night. COROVAS alleviates the associated fear of pain. Reduces the need for emergency nitroglycerin. Safe and effective for long-term therapy.

SUPPLIED—Boxes of 60 and 120.

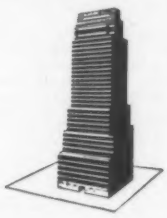
PROLONGED, SUSTAINED ACTION OF VASODILATING PENTAERYTHRITOL TETRANITRATE (PETN) 30 MG., AND SEDATIVE SECOBARBITURIC ACID 50 MG. IN EACH COROVAS TYMCAP.
As with all nitrates, use with caution in glaucoma.

AMFRE GRANT, INC.
Brooklyn 26, N. Y.


RECOVERY RATE: OVER 90%
... in over 1,000 published cases
of thromboembolic disease
"... at present, this is the oral anticoagulant of choice."1
- noncumulative
- rapid in action
- uniform in response
- convenient management of ambulatory patients
... safe and effective anticoagulant for long-term use..."2
Walker
100 TABLETS
HEDULIN
BRAND OF PHENINDIONE
50 mg.
CAUTION: Federal Law prohibits dispensing without prescription.
See enclosed circular for directions.
WALKER LABORATORIES, INC.

HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.



While at the American College of Cardiology meeting, May 16–19, be sure to visit McGraw-Hill booth "E" —On display will be:

New Volume V

Related Specialty Fields

CARDIOLOGY: An Encyclopedia of the Cardiovascular System

Sponsored by the American College of Cardiology
Edited by Aldo A. Luisada, M.D., Foreword by Ashton Graybiel, M.D.
2998 pp., $7^1/_4 \times 9^7/_8$, illus., set of Vols. I–IV—$100.00

VOLUME I: **Normal Heart and Vessels** contains a detailed analysis of the anatomy and physiology of the heart and vessels which serves as the basis for the other volumes in the set.

VOLUME II: **Methods** includes material on the Pulse, Percussion and Roentgenology, Functional Capacity, Blood Studies, Catheterization, and Cardiac Output.

VOLUME III: **Clinical Cardiology** describes the "heart" aspect of clinical cardiology and such topics as congenital, rheumatic, syphilitic, and coronary heart disease are covered.

VOLUME IV: **Clinical Cardiology—Therapy,** the second clinical volume, covers hypertension and hypertensive heart disease, angiology, heart failure, pulmonary edema, and various less common cardiovascular diseases.

VOLUME V: **Related Specialty Fields** is an outstanding volume written by forty-six international authorities. It relates much of the basic science material presented in earlier volumes to actual clinical practice, thereby completing the coverage of the all-important subject of cardiology. This fifth volume contains a most complete section on the pharmacology of cardiology, obstetric and surgical problems in cardiology, cardiovascular problems in pediatrics and geriatrics, medico-legal aspects of heart disease (including insurability and employment), and the effect of environment and physical exertion on the cardiovascular system. The fifth volume of this set is priced at $27.50, 612 pp., $7^1/_4 \times 9^7/_8$, illus.

TREATMENT OF CARDIOVASCULAR EMERGENCIES

By Aldo A. Luisada, M.D. and Leslie M. Rosa, M.D., 122 pp., $4^1/_8 \times 6^1/_2$, $4.95

This is a practical, short manual of use to all who are faced with cardiovascular emergencies. It clearly describes the immediate procedures and drugs used in cardiovascular and respiratory emergencies. Summaries at the beginning of each chapter further emphasize the reference value of this concise book.

THE PRACTICAL EVALUATION OF SURGICAL HEART DISEASE

The Glover Clinic, Written by Robert G. Trout, M.D.; Edited by Robert P. Glover, M.D., 132 pp., $8\frac{1}{2} \times 11$, 225 illus. (18 in color). Includes a 45 r.p.m. record of diagnostic heart murmurs, $10.00

This book is a practical, straightforward presentation of the diagnostic characteristics of various cardiac conditions which may be considered for surgical treatment.

The Blakiston Division
McGRAW-HILL BOOK COMPANY, Inc., 330 West 42nd St., New York 36, N. Y.

You may send me on a 10-day approval:

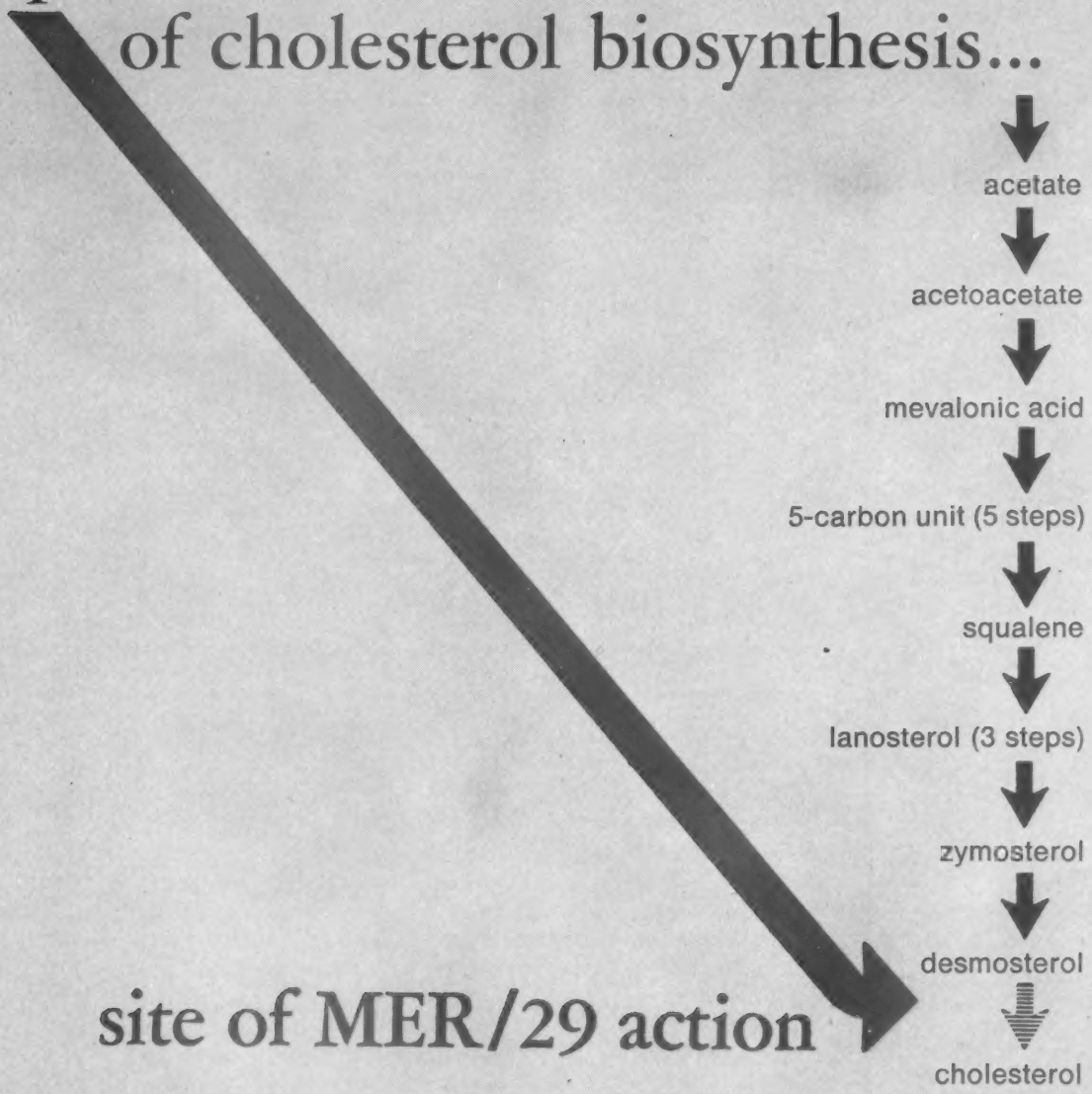
AUTHOR..... TITLE.....

NAME..... ADDRESS.....

CITY..... ZONE ..... STATE .....

AJC 5/61

specific[1], demonstrated[2] inhibition[3] of cholesterol biosynthesis...



1. The primary, the *only* known action of MER/29 is to lower the total body pool of sterols (serum and tissue); no effect on any other system or organ reported to date.

2. "Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-C^{14} was compared on and off MER/29. As much as a 50 per cent inhibition on MER/29 was observed in some patients."
—Steinberg, D.; Avigan, J., and Feigelson, E. B.: Circulation *22*:663 (Oct.) 1960.

3. "Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."
—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

...leading to specific, demonstrated advantages in cholesterol-lowering therapy

particularly in patients with coronary artery disease, generalized atherosclerosis, and other conditions thought to be associated with abnormal cholesterol metabolism

MER/29 REDUCES CHOLESTEROL IN AS MANY AS 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol without strict adherence to diet. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In patients with coronary artery disease, some of the concurrent benefits reported include decreased incidence and severity of anginal attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY: Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity and other conditions associated with cardiovascular disorders. These include nitroglycerin, PETN, and anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is *contraindicated in pregnancy.*

DOSAGE: One 250 mg. capsule daily, before breakfast.

SUPPLIED: Bottles of 30 pearl gray capsules.
Complete bibliography and product information available on request.

MER/29

(triparanol)

Merrell
SINCE 1828

The Wm. S. Merrell Company
Division of Richardson-Merrell Inc.
Cincinnati, Ohio • Weston, Ontario

Trademark: MER/29®

FOR ANGINA

Nitroglycerin is the drug of choice for the **ACUTE ATTACK**

'CARDILATE'

may well be chosen for **PROLONGED PROPHYLAXIS**

CLINICAL OPINION

"... the magnitude of the response to 15 mg. ['Cardilate'] was comparable to that following nitroglycerin.... The comparatively prolonged duration of action of erythrol tetranitrate when given sublingually makes it especially valuable for clinical use."[1]

CLINICAL OPINION

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most potent of all prophylactic agents available for the treatment of patients with angina pectoris."[2]

CLINICAL OPINION

"Erythrol tetranitrate exhibits an inherent long-acting vasodilating effect. Therefore it is the drug of choice in angina pectoris."[3]

'CARDILATE' brand
Erythrol Tetranitrate Sublingual Tablets

NEW

5 mg., scored

15 mg., scored

Bottles of 100 tablets.

Complete literature available on request.

1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

NEW 8th EDITION

MODERN DRUG ENCYCLOPEDIA

and Therapeutic Index with monthly supplement MODERN DRUGS

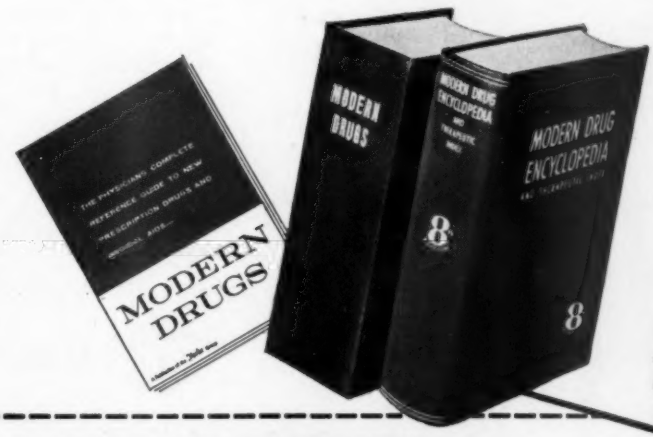
The only complete reference on new as well as established products.

Quickly answers questions about ethical pharmaceuticals.

MODERN DRUG ENCYCLOPEDIA, 8th Edition, an authoritative source of information on new and established pharmaceuticals. Gives you pertinent *facts* in concise form. Supplies facts you want to know to prescribe the new products with confidence. No struggle to keep cumbersome files up to date—just one compact bound volume and a compact binder for the monthly supplements.

MODERN DRUGS

A monthly supplement, with Robert S. Goodhart, M.D. as supervising editor, and John C. Helenore, Ph.G. as technical editor, supplies the same complete information on *new* pharmaceuticals as soon as they are available on your prescription. A convenient binder keeps the 24 issues together. Cumulative indices in *each* issue help you find *any* product listed in previous months.



THE PHYSICIAN'S REFERENCE LIBRARY IN ONE VOLUME KEPT UP-TO-DATE MONTHLY

ORDER YOUR MODERN DRUG ENCYCLOPEDIA TODAY

The Reuben H. Donnelley Corp., Publisher
MODERN DRUG ENCYCLOPEDIA
466 Lexington Avenue, New York 17, N.Y.

☐ Enclosed is $17.50* for my 8th Edition of MODERN DRUG ENCYCLOPEDIA and Therapeutic Index and the Monthly Supplement—MODERN DRUGS.

☐ Enclosed also is $3.50 for binder for MODERN DRUGS Monthly Supplement.

For delivery in N.Y.C., please include 3% Sales Tax with remittance.

Name_____

Address_____

City_____ Zone_____ State_____

U.S.A. $17.50 Foreign $23.50 (U.S. Currency)

Please make checks payable to The Reuben H. Donnelley Corporation

*Includes 2-year supplementary service at $5.00 per year ($6.00 Foreign)

acts directly on peripheral arterial walls . . . produces gradual, sustained vasodilatation without disturbing hemodynamics

CYCLOSPASMOL®

CYCLANDELATE

in peripheral vascular disease

Cyclospasmol is more effective in the treatment of arteriosclerosis obliterans and for the relief of intermittent claudication than sympatholytic and adrenergic blocking agents, because it acts directly on the arterial musculature.

- does not produce tachycardia, syncope or hypotension—may be used with safety in most patients having cerebral and coronary vascular diseases.
- dilates the deeper arteries as well as the superficial vessels to improve blood flow to the extremities.
- orally effective; produces a gradually increasing vasodilatation—aids in the healing of trophic leg ulcers.

Dosage: Usual dosage is two tablets (200 mg.) four times daily. Dosage range is from one to three tablets, q.i.d. Continued therapy and *individualized* dosage, depending upon response, is necessary for maximum effectiveness. Supply: 100 mg. tablets, bottles of 100.

References: 1. Council on Drugs, New and Nonofficial Drugs, J.A.M.A. *170*:1670, 1959. 2. Leslie, Robert E.: Effects of Cyclandelate (Cyclospasmol®) In Treatment of Circulatory Disturbances, Tex. J. Med. *56*:352-356, 1960. 3. Popkin, R. J.: Combined Vasodilator Therapy in Peripheral Vascular Diseases, J. Am. Geriatrics Soc. VIII: 638-643, 1960. 4. Van Wijk, T. W.: Angiology *4*:103, 1953. 5. Gillhespy, R. O.: Brit. M. J. *2*:1543, 1957. 6. Gillhespy, R. O.: Angiology *7*:27, 1956.

Professional literature and samples available on request

IVES IVES-CAMERON COMPANY
New York 16, N. Y.

*Trademark

Advertisers' Product Index

May, 1961

Abbott Laboratories
Enduron*.....*Insert facing page* 16

American Cystoscope Makers, Inc.
Cardiac Catheters..... 39

Amfre-Grant, Inc.
Corovas*..... 51

Beck-Lee Corp.
Cardiac Equipment..... 35

Best Foods, Div. Corn Products Co.
Mazola Oil..... 12

Bristol Laboratories, Div. Bristol-Myers Co.
Salutensin*.....36–37

Burroughs Wellcome & Co. (U.S.A.), Inc.
Cardilate*..... 56
Lanoxin*..... 16

Cambridge Instrument Co., Inc.
Cardiac Instruments..... 47

Carnation Company
Instant Milk..... 41

Cereal Institute, Inc.
Nutrient..... 50

Ciba Pharmaceutical Products, Inc.
Serpasil*-Apresoline*..... 27

F. A. Davis Co.
Medical Books..... 15

Endo Laboratories
Coumadin*..... 43

Geigy Company
Hygroton*..... 34
Sintrom*/Tromexan*..... 61

Ives-Cameron Company
Cyclospasmol*..... 58
Isordil*..... 33

Lafayette Pharmacal, Inc., Dist. by General Electric X-Ray
Electrell Cream..... 23

Lakeside Laboratories, Inc.
Mercuhydrin*/Metahydrin*..... 46

Lederle Laboratories, Div. American Cyanamid Co.
Diamox*..... 62

Thos. Leeming & Co., Inc.
Clarin*.....Third Cover

Eli Lilly & Company
Crystodigin*..... 38

McGraw Hill Book Co.
Medical Books..... 53

Merck Sharp & Dohme, Div. Merck & Co., Inc.
Aramine*.....28–29
Hydropres*.....44–45
Thrombolysin*.....20–21

The Wm. S. Merrell Company
Mer/29*.....54–55

Minneapolis-Honeywell
Electronic Medical Equipment..... 40

Ortho Pharmaceutical Corp.
Actase*.....Second Cover

Pitman-Moore, Div. of Allied Laboratories, Inc.
Emdee Margarine*..... 31

Purdue Frederick Co.
Cardioquin*..... 14

Riker Laboratories, Inc.
Rauwiloid*.....Fourth Cover

Roche Laboratories, Div. of Hoffmann-La Roche, Inc.
Marplan*..... 10

Sanborn Company
Cardiac Equipment..... 32

G. D. Searle & Co.
Aldactazide*..... 1

E. R. Squibb & Sons, Div. Mathieson Chemical Corp.
Pronestyl*..... 48
Theragran*..... 26

Walker Laboratories, Inc.
Hedulin*..... 52
Nicalex*..... 2

(Continued on next page)

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

Wallace Laboratories
Deprol* 30
Miltown* 8
Miltrate* 25

Warner-Chilcott Laboratories
Peritrate* 6

The Waters Corporation
Cardiac Equipment 49

Winthrop Laboratories
Dilcoron* 4

Wynn Pharmacal Corp.
Quinaglute* 24

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

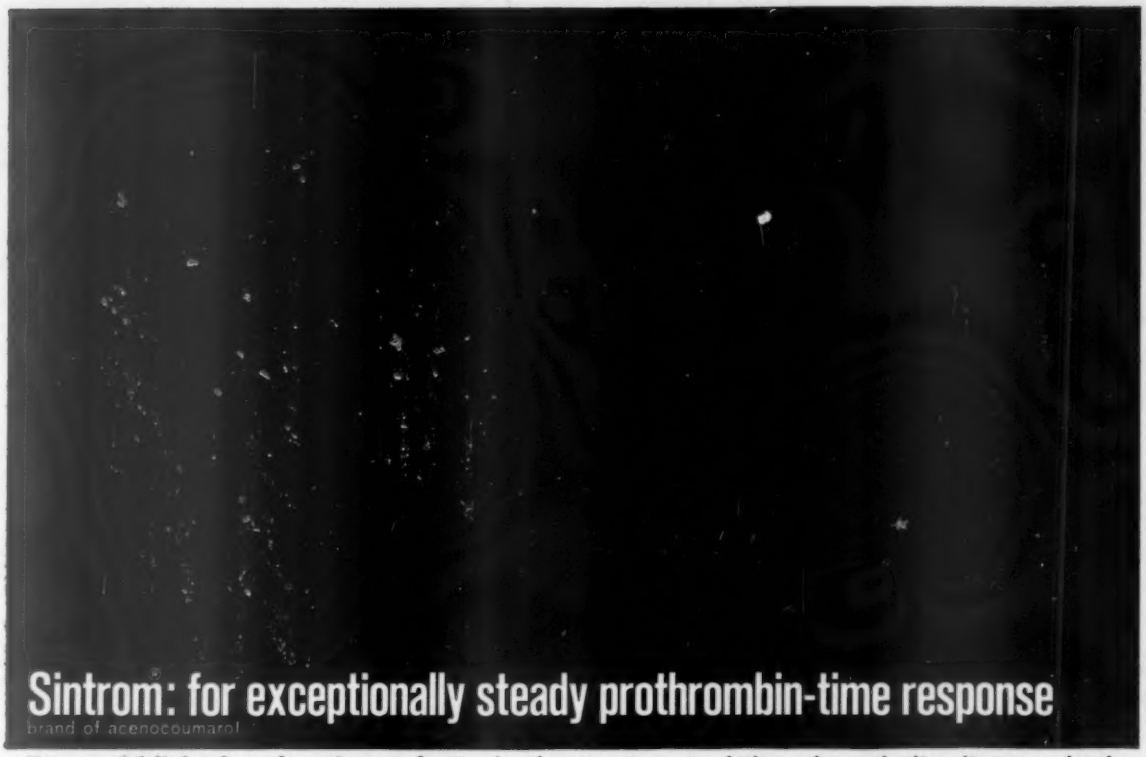
ADVERTISING REPRESENTATIVES

New York
P. D. Brewer, R. P. Davis,
L. F. LeJacq, J. S. Richards
Telephone ORegon 9-4000

San Francisco
Blanchard-Nichols Associates
Telephone YUkon 6-6341

Chicago
R. H. Andrew, C. P. Haffner
Telephone WAbash 2-7738

Los Angeles
Blanchard-Nichols Associates
Telephone DUnkirk 8-6134



Sintrom®: for exceptionally steady prothrombin-time response

brand of acenocoumarol

Two established oral anticoagulants. In the treatment of thromboembolic disease, both Sintrom and Tromexan reliably bring about hypoprothrombinemic response.

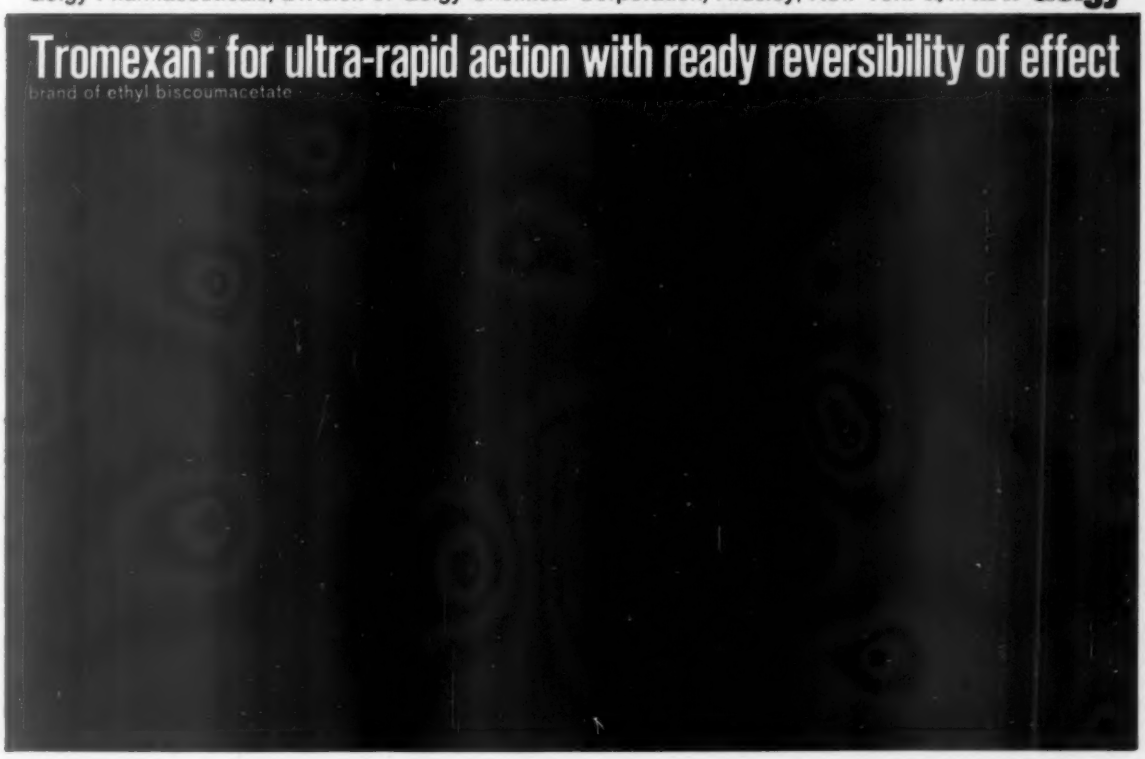
Distinguished by high potency and its ability to maintain a uniform response with a constant single daily dose, Sintrom is particularly suited to long-term therapy. Significantly more rapid and transient in action, Tromexan is well adapted to cases calling for more immediate control of thrombotic tendencies.

Full information regarding dosage, side effects, precautions and contraindications available on request.

Sintrom®, brand of acenocoumarol, is supplied as double-scored tablets of 4 mg.

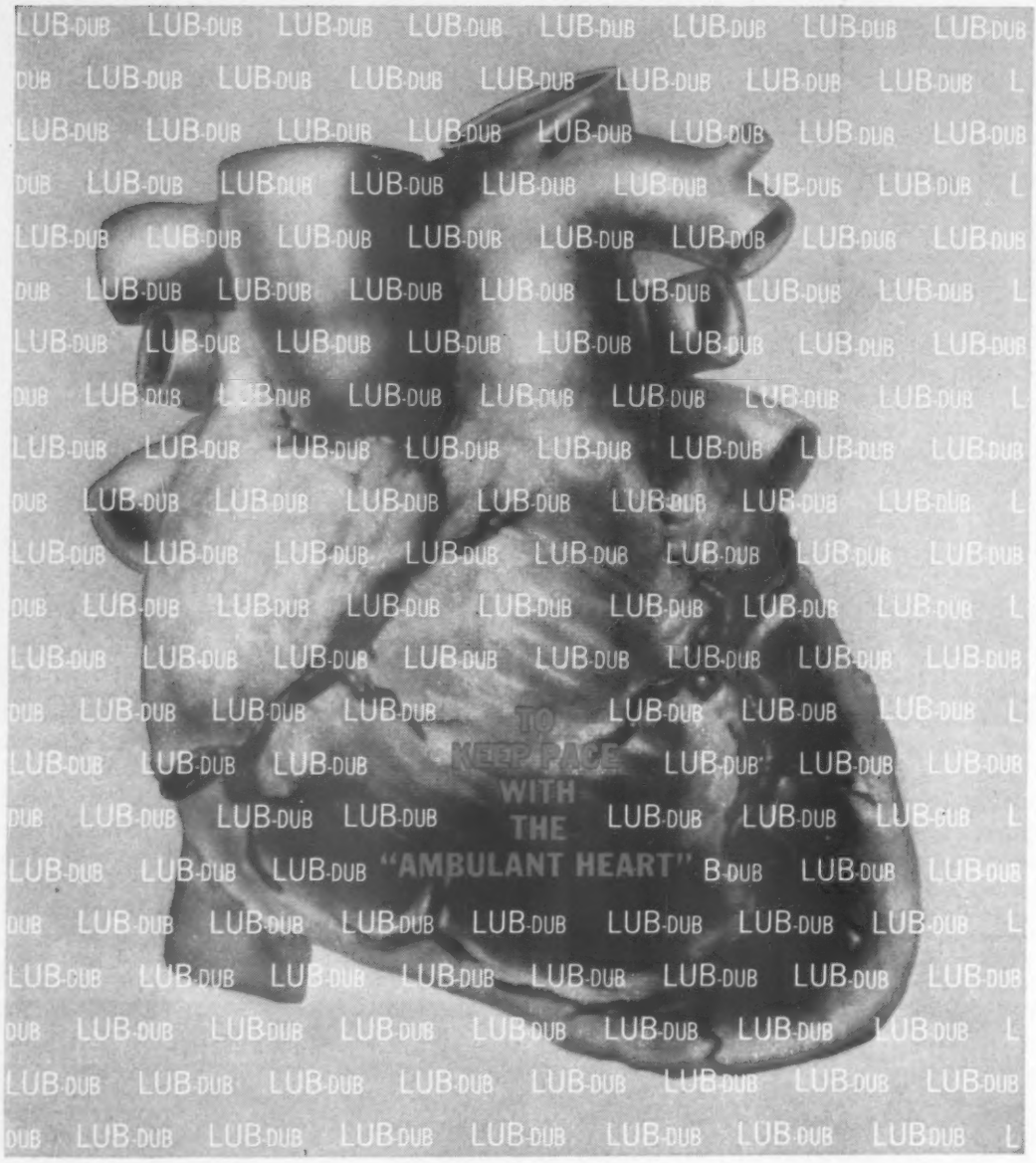
Tromexan®, brand of ethyl biscoumacetate, is supplied as single-scored tablets of 150 and 300 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York SI/TR-662-61 **Geigy**



Tromexan®: for ultra-rapid action with ready reversibility of effect

brand of ethyl biscoumacetate



DIAMOX®

ACETAZOLAMIDE LEDERLE

For gentle diuresis

In mild to moderate decompensation, DIAMOX closely matches diuretic action to diuretic needs. Gentle removal of water is achieved without distorting normal electrolyte ratios. A single morning dose provides comfortable, self-limiting daytime action and nighttime rest. Tablets of 250 mg. Parenteral, vials of 500 mg.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

If postcoronary management is
of special interest to you,
consider the demonstrated value
of sublingual heparin . . .

"In a controlled clinical study of 260 postcoronary patients, one-half were given sublingual heparin and one-half received conventional treatment. During the period of observation, averaging more than 2 years per patient, there were 12 recurrent infarctions in the heparin-treated group and 38 in the control group. This difference is statistically significant."

Fuller, H. L.: Angiology *11*:200 (June) 1960.

Simple and safe for long-term therapy, Clarin* (sublingual heparin) effectively controls the prolonged postprandial lipemia associated with atherosclerosis by facilitating the normal physiologic breakdown of fats. Unlike parenteral heparin, the use of Clarin requires no clotting-time or prothrombin determinations. The antilipemic activity of each manufactured lot of tablets is confirmed by sublingual control tests in animals.

Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient. *Dosage:* After each meal, hold one tablet under the tongue until dissolved. *Supplied:* Bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

An informative booklet, "Hyperlipemia, Heparin and Management of the Postcoronary Patient," is available from Thos. Leeming & Co., Inc., 155 East 44th St., New York 17, N. Y.

*Registered trade mark. Patent applied for.

Clarin
(sublingual heparin potassium, Leeming)

FEB 20 1964

Over 600,000,000 patient-days of effective, well-tolerated antihypertensive therapy...

Rauwiloid®

alseroxylon, 2 mg.

is still unexcelled

- Just two tablets at bedtime

Eight years of continuous use... prove enduring patient-acceptance and physician-satisfaction with RAUWILOID... *without any revisions of claims, changes of dosage, or additional side actions encountered.*

Rauwiloid is an original development of Riker Northridge, California